

R.50
EO(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
26 July 2001 (26.07.2001)

PCT

(10) International Publication Number
WO 01/53263 A1(51) International Patent Classification⁷: **C07D 213/74, 213/643, 213/80, 213/82, 239/48, 239/47, 487/04, 473/34, A61K 31/44, 31/52, 31/505, A61P 43/00 // (C07D 487/04, 235/00, 221/00)**

(21) International Application Number: PCT/IB01/00004

(22) International Filing Date: 5 January 2001 (05.01.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/176,611 18 January 2000 (18.01.2000) US

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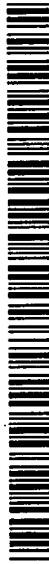
(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

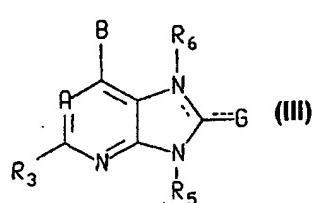
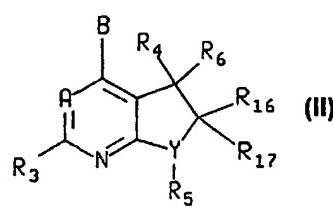
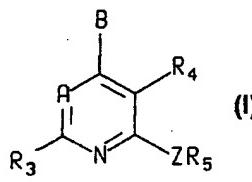
— with international search report

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(54) Title: CORTICOTROPIN RELEASING FACTOR ANTAGONISTS

WO 01/53263 A1.



(57) Abstract: Corticotropin-releasing factor (CRF) antagonists having the formulae (I), (II) or (III), wherein the dashed lines, A, B, Y, Z, G, R₃, R₄, R₅, R₆, R₁₆ and R₁₇ are as defined in the application, and processes for preparing them. These compounds and their pharmaceutically acceptable salts are useful in the treatment disorders including CNS and stress-related disorders.

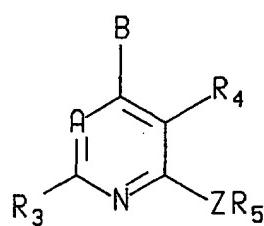
CORTICOTROPIN RELEASING FACTOR ANTAGONISTSBackground Of The Invention

This invention relates to pyridines, pyrimidines, purinones, pyrrolopyrimidinones and pyrrolopyridinones, processes for preparing them, pharmaceutical compositions containing them, and methods of using them to treat certain central nervous system (CNS) and other disorders.

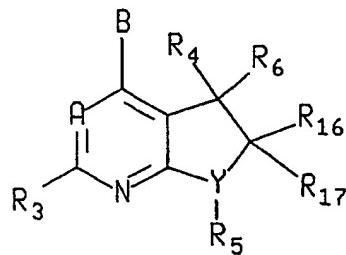
CRF antagonists are mentioned in U.S. Patents 4,605,642, issued August 12, 1986, and 5,063,245, issued November 5, 1991, referring to peptides and pyrazolinones, respectively. CRF antagonists are also described in U.S. Patent 5,962,479, issued October 5, 1999. The 10 importance of CRF antagonists is set out in the literature, e.g., as discussed in U.S. Patent 5,063,245, which is incorporated herein by reference. A recent outline of the different activities possessed by CRF antagonists is found in M. J. Owens et al., Pharm. Rev., Vol. 43, pages 425 to 473 (1991), also incorporated herein by reference. Based on the research described in these two and other references, CRF antagonists are effective in the treatment of a wide range of 15 stress-related illnesses, such as depression, anxiety, headache, irritable bowel syndrome, inflammatory diseases, immune suppression, Alzheimer's disease, gastrointestinal diseases, anorexia nervosa, hemorrhagic stress, drug and alcohol withdrawal symptoms, drug addiction, infertility, head trauma, stroke, and stress-induced infections in humans and animals. The use of CRF antagonists for treatment of Syndrome X has also been described in U.S. Patent 20 Application No. 09/696,822, filed October 26, 2000, and European Patent Application No. 00309441.4, filed October 26, 2000, which are also incorporated in their entireties herein by reference. Methods for using CRF antagonists to treat congestive heart failure are described in U.S. Serial No. 09/248,073, filed February 10, 1999, now U.S. Patent 6,043,260 (issued March 28, 2000) which is also incorporated herein in its entirety by reference.

Summary of the Invention

The present invention provides compounds of the formula

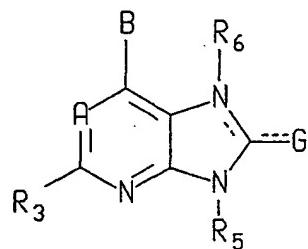


I



II

or



III

and pharmaceutically acceptable salts thereof, wherein

- 5 the dashed lines represent optional double bonds, with the proviso that when the dashed line in C—G represent a double bond, then the dashed line in N(R₆)—C does not represent a double bond; and with the proviso that when the dashed line in N(R₆)—C represents a double bond, R₆ is absent in formula III and the dashed line in C—G does not represent a double bond;

10 A is -CR₇ or N;

B is -NR₁R₂, -CR₁R₂R₁₁, -C(=CR₂R₁₂)R₁, -NHCHR₁R₂, -OCHR₁R₂, -SCHR₁R₂, -CHR₂OR₁, -CHR₁OR₂, -CHR₂SR₁, -C(S)R₂, -C(O)R₂, -CHR₂NR₁R₂, -CHR₁NHR₂, -CHR₁N(CH₃)R₂, or -NR₁₂NR₁R₂;

- when the dashed line in $\text{C}\text{—}\text{G}$ represents a double bond, then G is hydrogen, oxygen, sulfur, NH, or N(C₁-C₄ alkyl);
- when the dashed line in $\text{C}\text{—}\text{G}$ does not represent a double bond, then $\text{C}\text{—}\text{G}$ is -C(H)(NH₂), CH₂, -C(H)(methoxy), -C(H)(ethoxy), -C(H)(O(C₃-C₄ alkyl)), -C(H)(halo), -C(H)(trifluoromethoxy), -C(H)(methyl), -C(H)(ethyl), -C(H)(C₃-C₄ alkyl), -C(H)(S(C₁-C₄ alkyl)), -C(C₁-C₄ alkyl)(C₁-C₄ alkyl), cyclopropyl, -C(H)(cyclopropyl), thiomethoxy, -C(H)(NH₂), -C(H)(NHCH₃), -C(H)(N(CH₃)₂), or -C(H)(trifluoromethyl);
- wherein said cyclopropyl, methoxy, ethoxy, C₃-C₄ alkyl, and C₁-C₄ alkyl groups of $\text{C}\text{—}\text{G}$ may optionally be substituted by one OH, methoxy, or trifluoromethoxy, or may optionally be substituted by from one to six fluoro atoms;
- Y is CH or N;
- Z is NH, O, S, -N(C₁-C₂ alkyl), -NC(O)CF₃, or -C(R₁₃R₁₄), wherein R₁₃ and R₁₄ are each, independently, hydrogen, trifluoromethyl or methyl, or one of R₁₃ and R₁₄ is cyano and the other is hydrogen or methyl, or -C(R₁₃R₁₄) is a cyclopropyl group, or Z is nitrogen or CH and forms a five or six membered heterocyclic ring fused with R₅, which ring optionally comprises two or three further hetero members selected independently from oxygen, nitrogen, NR₁₂, and S(O)_m, and optionally comprises from one to three double bonds, and is optionally substituted with halo, C₁-C₄ alkyl, -O(C₁-C₄ alkyl), NH₂, NHCH₃, N(CH₃)₂, CF₃, or OCF₃, with the proviso that said ring does not contain any -S-S-, -S-O-, -N-S-, or -O-O- bonds, and does not comprise more than two oxygen or S(O)_m heterologous members;
- R₁ is -C(O)H, -C(O)(C₁-C₆ alkyl), -C(O)(C₁-C₆ alkylene)(C₃-C₈ cycloalkyl), -C(O)(C₃-C₈ cycloalkylene)(C₃-C₈ cycloalkyl), -C(O)(C₁-C₆ alkylene)(C₄-C₈ heterocycloalkyl), -C(O)(C₃-C₈ cycloalkylene)(C₄-C₈ heterocycloalkyl), -C₁-C₆ alkyl, -C₃-C₈ cycloalkyl, -C₄-C₈ heterocycloalkyl, -(C₁-C₆ alkylene)(C₃-C₈ cycloalkyl), -(C₃-C₈ cycloalkylene)(C₃-C₈ cycloalkyl), -(C₁-C₆ alkylene)(C₄-C₈ heterocycloalkyl), -(C₃-C₈ cycloalkylene)(C₄-C₈ heterocycloalkyl), or -O-aryl, or -O-(C₁-C₆ alkylene)-aryl; wherein said aryl, C₄-C₈ heterocycloalkyl, C₁-C₆ alkyl, C₃-C₈ cycloalkyl, C₃-C₈ cycloalkylene, and C₁-C₆ alkylene groups may each independently be optionally substituted with from one to six fluoro and may each independently be optionally substituted with one or two substituents R₈ independently selected from the group consisting of C₁-C₄ alkyl, -C₃-C₈ cycloalkyl, hydroxy, fluoro, chloro, bromo, iodo, CF₃, -O-(C₁-C₆ alkyl), -O-(C₃-C₅ cycloalkyl), -O-CO-(C₁-C₄ alkyl), -O-CO-NH(C₁-C₄ alkyl), -O-CO-N(R₂₄)(R₂₅), -N(R₂₄)(R₂₅), -S(C₁-C₄ alkyl), -S(C₃-C₅ cycloalkyl), -N(C₁-C₄ alkyl)CO(C₁-C₄ alkyl), -NHCO(C₁-C₄ alkyl), -COO(C₁-C₄ alkyl), -CONH(C₁-C₄ alkyl), -CON(C₁-C₄ alkyl)(C₁-C₂ alkyl), CN, NO₂, -OSO₂(C₁-C₄ alkyl), S⁺(C₁-C₆ alkyl)(C₁-C₂ alkyl)I⁻, -SO(C₁-C₄ alkyl) and -SO₂(C₁-C₄ alkyl); and wherein the C₁-C₆ alkyl, C₁-C₆ alkylene, C₅-C₈ cycloalkyl, C₅-C₈ cycloalkylene, and C₅-C₈ heterocycloalkyl moieties of R₁ may optionally independently contain from one to three double or triple bonds;

and wherein the C₁-C₄ alkyl moieties and the C₁-C₆ alkyl moieties of R₆ can optionally independently be substituted with hydroxy, C₁-C₄ alkyl, amino, aryl, -CH₂-aryl, -C₃-C₅ cycloalkyl, or -O-(C₁-C₄ alkyl), and can optionally independently be substituted with from one to five fluoro, and can optionally contain one or two double or triple bonds; and wherein each heterocycloalkyl group of R₁ contains from one to three heteromieties selected from oxygen, S(O)_m, nitrogen, and NR₁₂;

R₂ is hydrogen, C₁-C₁₂ alkyl, C₃-C₈ cycloalkyl, C₄-C₈ heterocycloalkyl, -(C₁-C₆ alkylene)(C₃-C₈ cycloalkyl), -(C₃-C₈ cycloalkylene)(C₃-C₈ cycloalkyl), -(C₁-C₆ alkylene)(C₄-C₈ heterocycloalkyl), -(C₃-C₈ cycloalkylene)(C₄-C₈ heterocycloalkyl), aryl, -(C₁-C₆ alkylene)aryl, or -(C₃-C₈ cycloalkylene)(aryl); wherein each of the foregoing R₂ groups may optionally be substituted with from one to three substituents independently selected from chloro, fluoro, and C₁-C₆ alkyl, wherein one of said one to three substituents can further be selected from bromo, iodo, C₁-C₆ alkoxy, -OH, -O-CO-(C₁-C₆ alkyl), -O-CO-N(C₁-C₄ alkyl)(C₁-C₂ alkyl), -S(C₁-C₆ alkyl), -S(O)(C₁-C₆ alkyl), -S(O)₂(C₁-C₆ alkyl), S⁺(C₁-C₆ alkyl)(C₁-C₂ alkyl)I⁻, CN, and NO₂; and wherein the C₁-C₁₂ alkyl, -(C₁-C₆ alkylene), -(C₅-C₈ cycloalkyl), -(C₅-C₈ cycloalkylene), and -(C₅-C₈ heterocycloalkyl) moieties of R₂ may optionally independently contain from one to three double or triple bonds; and wherein each heterocycloalkyl group of R₂ contains from one to three heteromieties selected from oxygen, S(O)_m, nitrogen, and NR₁₂;

or where R₁ and R₂ are as in -NHCHR₁R₂, -OCHR₁R₂, -SCHR₁R₂, -CHR₁R₂ or -NR₁R₂, R₁ and R₂ of B may form a saturated 5- to 8-membered ring which may optionally contain one or two double bonds and in which one or two of the ring carbons may optionally be replaced by an oxygen, S(O)_m, nitrogen or NR₁₂; and which carbocyclic ring can optionally be substituted with from 1 to 3 substituents selected from the group consisting of hydroxy, C₁-C₄ alkyl, fluoro, chloro, bromo, iodo, CF₃, -O-(C₁-C₄ alkyl), -O-CO-(C₁-C₄ alkyl), -O-CO-NH(C₁-C₄ alkyl), -O-CO-N(C₁-C₄ alkyl)(C₁-C₂ alkyl), -NH(C₁-C₄ alkyl), -N(C₁-C₂ alkyl)(C₁-C₄ alkyl), -S(C₁-C₄ alkyl), -N(C₁-C₄ alkyl)CO(C₁-C₄ alkyl), -NHCO(C₁-C₄ alkyl), -COO(C₁-C₄ alkyl), -CONH(C₁-C₄ alkyl), -CON(C₁-C₄ alkyl)(C₁-C₂ alkyl), CN, NO₂, -OSO₂(C₁-C₄ alkyl), -SO(C₁-C₄ alkyl), and -SO₂(C₁-C₄ alkyl), wherein one of said one to three substituents can further be selected from phenyl;

R₃ is methyl, ethyl, fluoro, chloro, bromo, iodo, cyano, methoxy, OCF₃, NH₂, NH(C₁-C₂ alkyl), N(CH₃)₂, -NHCOCF₃, -NHCH₂CF₃, S(O)_m(C₁-C₄ alkyl), CONH₂, -CONHCH₃, CON(CH₃)₂, -CF₃, or CH₂OCH₃;

R₄ is hydrogen, C₁-C₄ alkyl, C₃-C₅ cycloalkyl, -(C₁-C₄ alkylene)(C₃-C₅ cycloalkyl), -(C₃-C₅ cycloalkylene)(C₃-C₅ cycloalkyl), cyano, fluoro, chloro, bromo, iodo, -OR₂₄, C₁-C₆ alkoxy, -O-(C₃-C₅ cycloalkyl), -O-(C₁-C₄ alkylene)(C₃-C₅ cycloalkyl), -O-(C₃-C₅ cycloalkylene)(C₃-C₅ cycloalkyl), -CH₂SC(S)O(C₁-C₄ alkyl), -CH₂OCF₃, -CF₃, amino, nitro, -NR₂₄R₂₅, -(C₁-C₄

- alkylene)-OR₂₄, -(C₁-C₄ alkylene)Cl, -(C₁-C₄ alkylene)NR₂₄R₂₅, -NHCOR₂₄, -NHCONR₂₄R₂₅, -C=NOR₂₄, -NHNR₂₄R₂₅, -S(O)_mR₂₄, -C(O)R₂₄, -OC(O)R₂₄, -C(O)CN, -C(O)NR₂₄R₂₅, -C(O)NHR₂₄R₂₅, and -COOR₂₄, wherein the alkyl and alkylene groups of R₄ may optionally independently contain one or two double or triple bonds and may optionally independently be substituted with one or two substituents R₁₀ independently selected from hydroxy, amino, -NHCOCH₃, -NHCOCH₂Cl, -NH(C₁-C₂ alkyl), -N(C₁-C₂ alkyl)(C₁-C₂ alkyl), -COO(C₁-C₄ alkyl), -COOH, -CO(C₁-C₄ alkyl), C₁-C₆ alkoxy, C₁-C₃ thioalkyl, cyano and nitro, and with one to four substituents independently selected from fluoro and chloro;
- R₅ is aryl or heteroaryl and is substituted with from one to four substituents R₂₇ independently selected from halo, C₁-C₁₀ alkyl, -(C₁-C₄ alkylene)(C₃-C₈ cycloalkyl), -(C₁-C₄ alkylene)(C₄-C₈ heterocycloalkyl), -(C₃-C₈ cycloalkyl), -(C₄-C₈ heterocycloalkyl), -(C₃-C₈ cycloalkylene)(C₃-C₈ cycloalkyl), -(C₃-C₈ cycloalkylene)(C₄-C₈ heterocycloalkyl), C₁-C₄ haloalkyl, C₁-C₄ haloalkoxy, nitro, cyano, -NR₂₄R₂₅, -NR₂₄COR₂₅, -NR₂₄CO₂R₂₆, -COR₂₄, -OR₂₅, -CONR₂₄R₂₅, -CO(NOR₂₂)R₂₃, -CO₂R₂₆, -C=N(OR₂₂)R₂₃, and -S(O)_mR₂₃; wherein said C₁-C₁₀ alkyl, C₃-C₈ cycloalkyl, (C₁-C₄ alkylene), (C₃-C₈ cycloalkyl), (C₃-C₈ cycloalkylene), and (C₄-C₈ heterocycloalkyl) groups can be optionally substituted with from one to three substituents independently selected from C₁-C₄ alkyl, C₃-C₈ cycloalkyl, (C₁-C₄ alkylene)(C₃-C₈ cycloalkyl), -(C₃-C₈ cycloalkylene)(C₃-C₈ cycloalkyl), C₁-C₄ haloalkyl, hydroxy, C₁-C₆ alkoxy, nitro halo, cyano, -NR₂₄R₂₅, -NR₂₄COR₂₅, NR₂₄CO₂R₂₆, -COR₂₄, -OR₂₅, -CONR₂₄R₂₅, CO₂R₂₆, -CO(NOR₂₂)R₂₅, and -S(O)_mR₂₃; and wherein two adjacent substituents of the R₅ group can optionally form a 5-7 membered ring, saturated or unsaturated, fused to R⁵, which ring optionally can contain one, two, or three heterologous members independently selected from O, S(O)_m, and N, but not any -S-S-, -O-O-, -S-O-, or -N-S- bonds, and which ring is optionally substituted with C₁-C₄ alkyl, C₃-C₈ cycloalkyl, -(C₁-C₄ alkylene)(C₃-C₈ cycloalkyl), -(C₃-C₈ cycloalkylene)(C₃-C₈ cycloalkyl), C₁-C₄ haloalkyl, nitro, halo, cyano -NR₂₄R₂₅, NR₂₄COR₂₅, NR₂₄CO₂R₂₆, -COR₂₄, -OR₂₅, -CONR₂₄R₂₅, CO₂R₂₆, -CO(NOR₂₆)R₂₅, or -S(O)_mR₂₃; wherein one of said one to four optional substituents R₂₇ can further be selected from -SO₂NH(C₁-C₄ alkyl), -SO₂NH(C₁-C₄ alkylene)(C₃-C₈ cycloalkyl), -SO₂NH(C₃-C₈ cycloalkylene)(C₃-C₈ cycloalkyl), -SO₂N(C₁-C₄ alkyl)(C₁-C₂ alkyl), -SO₂NH₂, -NHSO₂(C₁-C₄ alkyl), -NHSO₂(C₃-C₈ cycloalkyl), -NHSO₂(C₁-C₄ alkylene)(C₃-C₈ cycloalkyl), and -NHSO₂(C₃-C₈ cycloalkylene)(C₃-C₈ cycloalkyl); and wherein the alkyl, and alkylene groups of R₅ may independently optionally contain one double or triple bond;
- R₆ is hydrogen, C₁-C₆ alkyl, C₃-C₈ cycloalkyl, -(C₁-C₆ alkylene)(C₃-C₈ cycloalkyl), or -(C₃-C₈ cycloalkylene)(C₃-C₈ cycloalkyl), wherein said alkyl and cycloalkyl may optionally be substituted with one hydroxy, methoxy, ethoxy or fluoro group;

or, wherein the compound is a compound of formula II, R₆ and R₄ can together form an oxo (=O) group or can be connected to form a 3-8 membered carbocyclic ring, optionally containing one to three double bonds, and optionally containing one, two, or three heterologous ring members selected from O, SO_m, N, and NR₁₂, but not containing any -O-O-, -S-O-, -S-S-, or -N-S- bonds, and further optionally substituted with C₁-C₄ alkyl or C₃-C₈ cycloalkyl, wherein said C₁-C₄ alkyl substituent may optionally contain one double or triple bond;

R₇ is hydrogen, methyl, fluoro, chloro, bromo, iodo, cyano, hydroxy, -O(C₁-C₂ alkyl), -O(cyclopropyl), -COO(C₁-C₂ alkyl), -COO(C₃-C₈ cycloalkyl), -OCF₃, CF₃, -CH₂OH, or CH₂OCH₃;

R₁₁ is hydrogen, hydroxy, fluoro, ethoxy, or methoxy;

10 R₁₂ is hydrogen or C₁-C₄ alkyl;

R₁₆ and R₁₇ are each, independently, hydrogen, hydroxy, methyl, ethyl, methoxy, or ethoxy, except that R₁₆ and R₁₇ are not both methoxy or ethoxy;

or R₁₆ and R₁₇ together form an oxo (=O) group;

15 or R₁₆ and R₁₇ are connected to form a 3-8 membered carbocyclic ring, optionally containing one to three double bonds, and optionally containing from one to three heterologous ring members selected from O, SO_m, N, and NR₁₂, but not containing any -O-O-, -S-O-, -S-S-, or -N-S- bonds, and further optionally substituted with C₁-C₄ alkyl or C₃-C₈ cycloalkyl, wherein said C₁-C₄ alkyl substituent may optionally contain one double or triple bond;

R₂₂ is independently at each occurrence selected from hydrogen, C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₃-C₈ alkenyl, C₃-C₈ alkyanyl, C₃-C₈ cycloalkyl, (C₃-C₈ cycloalkylene)(C₃-C₈ cycloalkyl), and (C₁-C₄ alkylene)(C₃-C₈ cycloalkyl);

20 R₂₃ is independently at each occurrence selected from C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₂-C₈ alkoxyalkyl, C₃-C₈ cycloalkyl, -(C₁-C₄ alkylene)(C₃-C₈ cycloalkyl), -(C₃-C₈ cycloalkylene)(C₃-C₈ cycloalkyl), aryl, -(C₁-C₄ alkylene)aryl, piperidine, pyrrolidine, piperazine, N-methylpiperazine, 25 morpholine, and thiomorpholine;

R₂₄ and R₂₅ are independently at each occurrence selected from hydrogen, -C₁-C₄ alkyl, C₁-C₄ haloalkyl, especially CF₃, -CHF₂, CF₂CF₃, or CH₂CF₃, -(C₁-C₄ alkylene)OH, -(C₁-C₄ alkylene)-O-(C₁-C₄ alkyl), -(C₁-C₄ alkylene)-O-(C₃-C₅ cycloalkyl), C₃-C₈ cycloalkyl, -(C₁-C₄ alkylene)(C₃-C₈ cycloalkyl), -(C₃-C₈ cycloalkylene)(C₃-C₈ cycloalkyl), -(C₄-C₈ heterocycoalkyl), 30 -(C₁-C₄ alkylene)(C₄-C₈ heterocycoalkyl), -(C₃-C₈ cycloalkylene)(C₄-C₈ heterocycoalkyl), aryl, and -(C₁-C₄ alkylene)(aryl), wherein the -C₄-C₈ heterocycoalkyl groups can each independently optionally be substituted with aryl, CH₂-aryl, or C₁-C₄ alkyl, and can optionally contain one or two double or triple bonds; or, when R₂₄ and R₂₅ are as NR₂₄R₂₅, -C(O)NR₂₄R₂₅, -(C₁-C₄ alkylene)NR₂₄R₂₅, or -NHCONR₂₄R₂₅, then NR₂₄R₂₅ may further optionally form a 4 to 8 35 membered heterocyclic ring optionally containing one or two further hetero members

independently selected from $S(O)_m$, oxygen, nitrogen, and NR_{12} , and optionally containing from one to three double bonds;

R_{25} is independently at each occurrence selected from C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_3-C_8 cycloalkyl, $-(C_1-C_4)$ alkylene)(C_3-C_8 cycloalkyl), $-(C_3-C_8)$ cycloalkylene)(C_3-C_8 cycloalkyl), aryl, 5 and $-(C_1-C_4)$ alkylene)(aryl); and

wherein each m is independently zero, one, or two,

with the proviso that heterocycloalkyl groups of the compound of formula I, II, or III do not comprise any $-S-S-$, $-S-O-$, $-N-S-$, or $-O-O-$ bonds, and do not comprise more than two oxygen or $S(O)_m$ heterologous members.

10 In one embodiment, the invention provides compounds of formula I or II, wherein R_4 is $-NHCH_2CF_3$, $-CONHNH_2$, $-CONHNHCH_3$. In another embodiment R_4 is $-OCF_3$ or fluoro. In another embodiment R_4 is $-OCHF_2$.

In another embodiment, the invention provides compounds of formula I or II, preferably formula I, wherein R_4 is $-C(O)NR_{24}R_{25}$ or $-C(O)NHNR_{24}R_{25}$. In a preferred 15 embodiment, R_4 is $-C(O)NR_{24}R_{25}$. If R_4 is $-C(O)NR_{24}R_{25}$ or $-C(O)NHNR_{24}R_{25}$, then R_{24} and R_{25} are in a more particular embodiment selected independently from hydrogen and $-C_1-C_4$ alkyl. In another embodiment, R_4 is $-C(O)NH_2$ or $-C(O)NHCH_3$. In another embodiment, R_4 is $-C(O)N(CH_3)_2$.

20 In another more particular embodiment, the invention provides a compound of formula I, or II, preferably I, as defined above, wherein R_4 is $-C(O)NHCH_2(C_3-C_5)$ cycloalkyl, $-C(O)NH(C_3-C_5)$ cycloalkyl, $-C(O)N(C_3-C_5)$ cycloalkyl $_2$, $-C(O)NR_{24}R_{25}$ wherein R_{24} and R_{25} form a 4, 5, or 6 membered heterocyclic ring, $-C(O)NH(C_4-C_8)$ heterocycloalkyl, or $-C(O)NH(CH_2(C_4-C_8)$ heterocycloalkyl).

25 In another embodiment, the invention provides a compound of formula I or II, preferably formula I, wherein R_4 is $-(C_1-C_4)$ alkylene) $NR_{24}R_{25}$. If R_4 is $-(C_1-C_4)$ alkylene) $NR_{24}R_{25}$, then R_{24} and R_{25} are in a more particular embodiment selected independently from hydrogen, $-C_1-C_4$ alkyl, $-(C_1-C_4)$ alkylene)(C_3-C_8 cycloalkyl), and C_3-C_8 cycloalkyl.

30 In another embodiment, the invention provides a compound of formula I or II as defined above, wherein R_4 is $-OCH_2(C_3-C_5)$ cycloalkyl, $-O(C_3-C_5)$ cycloalkyl, $-SCH_2(C_3-C_5)$ cycloalkyl, or $-S(C_3-C_5)$ cycloalkyl.

In another embodiments of the invention, a compound of formula I or II, preferably I, as defined above, is provided, wherein R_4 is $-COOCH_3$. In another embodiment of the invention, a compound of formula I or II, preferably I, is provided wherein R_4 is $-COOCH_2CH_3$.

35 Another embodiment of the invention provides compounds of formula I or II, preferably I, as defined above, wherein R_4 is $-OCH_3$. In another embodiment of the invention,

compounds of formula I or II are provided, wherein R₄ is -CH₃. In another embodiment, R₄ is -CH₂CH₃. In another embodiment R₄ is chloro. In another embodiment, R₄ is bromo.

In another embodiment, a compound of formula I or II, preferably I, is provided, wherein R₄ is -CF₃.

5 In another embodiment, a compound of formula I or II, preferably I, is provided, wherein R₄ is -CH₂OH.

In another embodiment, a compound of formula I or II, preferably I, is provided, wherein R₄ is -CH₂OCH₃.

10 In another embodiment, a compound of formula I or II, preferably I, is provided, wherein R₄ is -CH₂OCF₃.

In another embodiment of the invention, the compound of formula I or II, preferably I, is as defined above, and R₄ is -SCH₃.

In another embodiment, a compound of formula I or II, preferably I, is provided, wherein R₄ is -S(O)CH₃.

15 In another embodiment, a compound of formula I or II, preferably I, is provided, wherein R₄ is -S(O)₂CH₃.

In another embodiment, a compound of formula I or II, preferably I, is provided, wherein R₄ is -C(O)CH₃.

20 In another embodiment, a compound of formula I or II, preferably I, is provided, wherein R₄ is -NR₂₄R₂₅. Preferably, R₂₄ and R₂₅ are C₁-C₄ alkyl or hydrogen. In a more particular embodiment, R₄ is -NH₂, -NHCH₃, or -N(CH₃)₂.

In another embodiment, a compound of formula I or II, preferably I, is provided, wherein R₄ is -NO₂.

25 In another embodiment, a compound of formula I or II, preferably I, is provided, wherein R₄ is -CH(OH)CH₃.

In another embodiment, a compound of formula I or II, preferably I, is provided, wherein R₄ is -CN.

30 In another embodiment, the invention provides compounds of formula I, II, or III as defined above, wherein B is -NR₁R₂, or -NHCHR₁R₂. If B is -NR₁R₂, R₁ is preferably C₁-C₆ alkyl, C₃-C₈ cycloalkyl, or -(C₁-C₆ alkylene)(C₃-C₈ cycloalkyl), more preferably -(C₁-C₆ alkylene)(C₃-C₈ cycloalkyl), and R₂ is preferably C₁-C₁₂ alkyl optionally containing from one to three double or triple bonds and optionally substituted with from one to three fluoro atoms. Preferably, B is -N(CH₂-cyclopropyl)(CH₂CH₃) or -N(CH₂-cyclopropyl)(CH₂CF₃).

If B is -NHCHR₁R₂, then R₁ is preferably -C(O)H, -C(O)(C₁-C₆ alkyl), or -C₁-C₆ alkyl, 35 wherein said C₁-C₆ alkyl is optionally substituted with from one to six fluoro atoms or one or two R₈ independently selected from -C₁-C₄ alkyl, hydroxy and -O-(C₁-C₆ alkyl), and R₂ is

- preferably $-C_1-C_{12}$ alkyl optionally containing from one to three double or triple bonds and optionally substituted with from one to three substituents selected from fluoro and C_1-C_8 alkyl. Preferably, if B is $-NHCHR_1R_2$, then R_1 is independently selected from $-CH_2CH_3$ and $-CF_2CH_3$, and R_2 is independently selected from $-CH_2CH_3$, $-CF_2CH_3$, $-CH(OH)CH_3$, $-CH(OCH_3)CH_3$, $-C(OH)(CH_3)_2$, and $-C(O)CH_3$. Preferably B is $-NHCH(CH_2CH_3)_2$, $-NHCH(CH_2CH_3)(CF_2CH_3)$, $-NHCH(CF_2CH_3)_2$, $-NHCH(CH(OH)CH_3)(CF_2CH_3)$, $-NHCH(CH(OCH_3)CH_3)(CH_2CH_3)$, $-NHCH(C(O)CH_3)(CH_2CH_3)$, $-NHCH(C(O)CH_3)(CF_2CH_3)$, $-NHCH(C(OH)(CH_3)_2)(CH_2CH_3)$, or $-NHCH(C(OH)(CH_3)_2)(CF_2CH_3)$.
- 10 ore preferably, B is $-N(CH_2\text{-cyclopropyl})(CH_2CH_3)$, $-NHCH(CH_2CH_3)_2$, $-NHCH(CH(OH)CH_3)(CF_2CH_3)$, $-NHCH(CH(OH)CH_3)(CH_2CH_3)$, $-NHCH(C(O)CH_3)(CH_2CH_3)$, or $-NHCH(C(OH)(CH_3)_2)(CH_2CH_3)$.
- In another embodiment of the invention, B is selected from $-OCHR_1R_2$, $SCHR_1R_2$, $-CHR_1NHR_2$, $-CHR_1N(CH_3)R_2$, $-CHR_2OR_1$, and $-CHR_1OR_2$.
- 15 In another embodiment of the invention, a compound of formula I, II, or III as defined above is provided, wherein R_3 is methyl, ethyl, $O-CH_3$, $-OCF_3$, Cl, $S-CH_3$, or CF_3 . Preferably R_3 is methyl.
- In another embodiment of the invention, a compound of formula III as defined above
- 20 is provided wherein the dashed line in $C\text{---}N(R_6)$ represents a double bond, and the dashed line in $C\text{---}G$ does not represent a double bond, and $C\text{---}G$ is CH_2 , $C(H)(CH_3)$, or $C(H)(CH_2CH_3)$.
- In another embodiment of the invention, a compound of formula III is provided, wherein the dashed line in $C\text{---}G$ represents a double bond, and $C\text{---}G$ is $C=O$, $C=S$, or
- 25 $C=NH$, and $C\text{---}N(R_6)$ is $C-NH$ or $C-N(C_1-C_4\text{ alkyl})$.
- In another embodiment of the invention, a compound of formula II as defined above is provided, wherein $CR_{16}R_{17}$ and CR_4R_6 are each independently selected from $-C=O$, $-CH_2$, $-CH(C_1-C_4\text{ alkyl})$, $-C(C_1-C_2\text{ alkyl})_2$, cyclopropyl, $-CHOH$, $-CHOCH_3$, $-C(OCH_2CH_2)$, and $-C(CH_2OCH_2)$.
- 30 In another embodiment, a compound of formula II is provided, wherein $CR_{16}R_{17}$ is selected from $-CH_2$, $-CH(C_1-C_4\text{ alkyl})$, $-C(C_1-C_2\text{ alkyl})_2$, cyclopropyl, $-CHOH$, and $-CHOCH_3$, and CR_4R_6 is $C=O$, CH_2 , $CH(C_1-C_2\text{ alkyl})$, or $-CHOCH_3$.
- In another embodiment of the invention, a compound of formula I, II, or III as defined above is provided, wherein R_5 is optionally substituted aryl or heteroaryl selected from
- 35 optionally substituted phenyl, thiazolyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, quinazolinyl, quinoxalinyl, pyrazinyl, pyrimidinyl, indazolyl, imidazolyl, furanyl, benzimidazolyl,

benzofuranyl, benzothiazolyl, benzisoxazolyl, isothiazolyl, pyrazolyl, pyrrolyl, indolyl, pyrrolopyridyl, oxazolyl, benzoxazolyl, benzothiadiazolyl, pyridyl, benzo[1,3]dioxolyl, and 2,3-dihydro-benzo[1,4]dioxinyl.

In another embodiment, R₅ is substituted with from one to four R₂₇ selected independently from C₁-C₄ alkyl, -O-(C₁-C₄ alkyl), chloro, bromo, -CH(CH₃)(OH), -C(CH₃)₂(OH), -CH(CH₃)(OCH₃), -C(CH₃)₂(OCH₃), OCF₃, OCHF₂, -O-cyclopropyl, -(CH₂-cyclopropyl, -CH(CF₃)(OH), -CH(CF₃)(OCH₃), -C(=O)(CF₃), -2-cyclopropyl-1-OH, 1-cyclopropyl-2-OH, -1-cyclopropyl-1-NH₂, -O-oxetanyl, -O-tetrahydrofuranyl, cyclopropyl, and -SCH₃.

10 In another embodiment of the invention, a compound of formula I, II, or III as defined above is provided, wherein R₅ is phenyl, pyridyl or pyrimidyl, substituted with two or three R₂₇ groups. In a more particular embodiment, R₅ is phenyl, substituted with two or three R₂₇ groups.

15 In another embodiment, a compound of formula I, II or III, preferably I, as defined above is provided, wherein R₅ is phenyl, pyridyl or pyrimidyl, substituted with two or three R₂₇ groups selected from halo, -(C₁-C₄)haloalkyl, -C(O)R₂₄, -OR₂₅, -C(O)NR₂₄R₂₅, and C₁-C₁₀ alkyl which is optionally substituted with one to three substituents, preferably one substituent, selected from hydroxy, C₁-C₆ alkoxy, and -NR₂₄R₂₅. Preferably, each R₂₇ is independently selected from methyl, ethyl, -CF₃, -OCH₃, -OCF₃, -C(O)NH₂, -C(O)NHCH₃, -C(O)CF₃, -C(O)CH₃, -CH(OH)CH₃, chloro, bromo, fluoro, -OCH₂CH₃, -O-cyclopropyl, -CH₂NH₂, -CH₂NHCH₃, -CH₂N(CH₃)₂, -CH₂OCH₃, and -CH(OCH₃)CH₃. More preferably, each R₂₇ is independently selected from methyl, ethyl, -CF₃, -OCH₃, -OCF₃, -C(O)NH₂, -C(O)NHCH₃, chloro, bromo, and fluoro.

20 In another embodiment, a compound of formula I, II or III, preferably I, is provided, wherein - is phenyl and is substituted with two or three substituents R₂₇ independently selected from methyl, chloro, -OCH₃, -OCF₃, bromo, and -C(O)NH₂.

In another embodiment of the invention, a compound of formula I as defined above is provided, wherein Z is O, NH, or NC(=O)CF₃. Preferably Z is O.

25 In a preferred embodiment of the invention, a compound of formula I is provided, wherein Z is O; B is -NHCHR₁R₂, wherein R₁ is preferably -C(O)H, -C(O)(C₁-C₆ alkyl), or -C₁-C₆ alkyl, wherein said C₁-C₆ alkyl is optionally substituted with from one to six fluoro atoms or one or two R₈ independently selected from -C₁-C₄ alkyl, hydroxy and -O-(C₁-C₆ alkyl), and wherein R₂ is preferably -C₁-C₁₂ alkyl optionally containing from one to three double or triple bonds and optionally substituted with from one to three substituents selected from fluoro and C₁-C₆ alkyl; R₅ is R₅ is phenyl, pyridyl or pyrimidyl, substituted with two or three R₂₇ groups selected from halo, -(C₁-C₄)haloalkyl, -C(O)R₂₄, -OR₂₅, -C(O)NR₂₄R₂₅, and C₁-C₁₀ alkyl which

is optionally substituted with one to three substituents, preferably one substituent, selected from hydroxy, C₁-C₆ alkoxy, and -NR₂₄R₂₅; and R₄ is -C(O)NR₂₄R₂₅. R₂₄ and R₂₅ of -C(O)NR₂₄R₂₅ are in a more particular embodiment selected independently from hydrogen and -C₁-C₄ alkyl.

5 In another preferred embodiment of the invention, a compound of formula I is provided, wherein Z is O; B is -NHCHR₁R₂, wherein R₁ of -NHCHR₁R₂ is preferably -C(O)H, -C(O)(C₁-C₆ alkyl), or -C₁-C₆ alkyl, wherein said C₁-C₆ alkyl is optionally substituted with from one to six fluoro atoms or one or two R₈ independently selected from -C₁-C₄ alkyl, hydroxy and -O-(C₁-C₆ alkyl), and wherein R₂ of -NHCHR₁R₂ is preferably -C₁-C₁₂ alkyl optionally containing from one to three double or triple bonds and optionally substituted with from one to three substituents selected from fluoro and C₁-C₆ alkyl; R₆ is R₅ is phenyl, pyridyl or pyrimidyl, substituted with two or three R₂₇ groups selected from halo, -(C₁-C₄ haloalkyl), -C(O)R₂₄, -OR₂₅, -C(O)NR₂₄R₂₅, and C₁-C₁₀ alkyl which is optionally substituted with one to three substituents, preferably one substituent, selected from hydroxy, C₁-C₆ alkoxy, and -NR₂₄R₂₅;

10 and R₄ is -NR₁R₂, wherein R₁ of -NR₁R₂ is preferably C₁-C₆ alkyl, C₃-C₈ cycloalkyl, or -(C₁-C₆ alkylene)(C₃-C₈ cycloalkyl), more preferably -(C₁-C₆ alkylene)(C₃-C₈ cycloalkyl), and R₂ of -NR₁R₂ is preferably C₁-C₁₂ alkyl optionally containing from one to three double or triple bonds and optionally substituted with from one to three fluoro atoms. Preferably, B is -N(CH₂-cyclopropyl)(CH₂CH₃) or -N(CH₂-cyclopropyl)(CH₂CF₃).

15

20 Examples of preferred compounds of this invention are:

2-(4-Chloro-2,6-dimethyl-phenoxy)-4-(1-hydroxymethyl-propylamino)-6,N-dimethyl-nicotinamide;

2-(4-Chloro-2,6-dimethyl-phenoxy)-4-(1-methoxymethyl-propylamino)-6,N-dimethyl-nicotinamide;

25 2-(4-Chloro-2,6-dimethyl-phenoxy)-4-(1-methoxymethyl-propylamino)-6-methyl-nicotinamide;

2-(4-Bromo-2-methoxy-phenoxy)-4-(1-ethyl-propylamino)-6-methyl-nicotinamide;

2-(4-Chloro-2,6-dimethyl-phenoxy)-4-(1-ethyl-2-methoxy-propylamino)-6-methyl-nicotinamide;

30 2-(4-Chloro-2,6-dimethyl-phenoxy)-4-(1-ethyl-2-methoxy-propylamino)-6,N-dimethyl-nicotinamide;

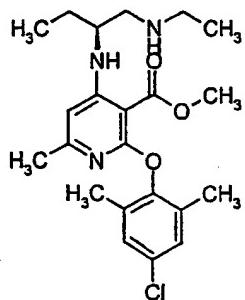
2-(4-Chloro-2-trifluoromethoxy-phenoxy)-4-(1-ethyl-propylamino)-6-methyl-nicotinamide;

35 2-(4-Chloro-2-trifluoromethoxy-phenoxy)-4-(1-ethyl-propylamino)-6-N-dimethyl-nicotinamide;

- 2-(4-Chloro-2,6-dimethyl-phenoxy)-4-(1S,2R-1-ethyl-2-methoxy-propylamino)-6,N-dimethyl-nicotinamide; and
2-(4-Chloro-2,6-dimethyl-phenoxy)-4-(1S,2S-1-ethyl-2-methoxy-propylamino)-6,N-dimethyl-nicotinamide;
- 5 and pharmaceutically acceptable salts thereof.
Other examples of preferred compounds of the invention are:
2-(4-Bromo-2-methoxy-phenoxy)-4-(1-ethyl-propylamino)-6-methyl-nicotinonitrile;
4-[4-(1-Ethyl-propoxy)-3,6-dimethyl-pyridin-2-yloxy]-3,5-dimethyl-benzamide;
2-(4-Chloro-2,6-dimethyl-phenoxy)-6-methyl-4-(1-methylsulfanyl methyl-propylamino)-
- 10 nicotinic acid methyl ester;
2-(4-Chloro-2,6-dimethyl-phenoxy)-4-(1-hydroxymethyl-propylamino)-6-methyl-nicotinic acid methyl ester;
2-(4-Bromo-2,6-dimethyl-phenoxy)-4-(1-ethyl-propylamino)-6-methyl-nicotinonitrile;
2-(4-Chloro-2-trifluoromethoxy-phenoxy)-4-(1-ethyl-propylamino)-6-methyl-nicotinic
15 acid methyl ester; and
2-(4-Chloro-2,6-dimethyl-phenoxy)-6-methyl-4-(tetrahydro-furan-3-ylamino)-nicotinic acid methyl ester; and pharmaceutically acceptable salts thereof.
- Other examples of compounds of the invention are:
20 2-(4-bromo-2-methyl-phenylamino)-4-(1-ethyl-propoxy)-6-methyl-nicotinic acid;
[2-(4-bromo-2-methyl-phenylamino)-4-(1-ethyl-propoxy)-6-methyl-pyridin-3-yl]-methanol;
2-(4-chloro-2,6-dimethyl-phenoxy)-4-(1-hydroxymethyl-propylamino)-6-methyl-nicotinic acid;
25 2-(4-chloro-2,6-dimethyl-phenoxy)-4-(1-hydroxymethyl-propylamino)-6-methyl-nicotinamide;
2-(4-chloro-2,6-dimethyl-phenoxy)-N-ethyl-4-(1-hydroxymethyl-propylamino)-6-methyl-nicotinamide;
2-(4-chloro-2,6-dimethyl-phenoxy)-4-(1-hydroxymethyl-propylamino)-6,N-dimethyl-nicotinamide;
30 cyclopropylmethyl-[2,5,6-trimethyl-7-(2,4,6-trimethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-amine;
cyclopropylmethyl-[3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-ethyl-amine;

✓ →

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2-(4-chloro-2,6-dimethyl-phenoxy)-4-(1-methoxycarbonyl-propylamino)-6-methyl-nicotinic acid methyl ester;

5 2-(4-chloro-2,6-dimethyl-phenoxy)-4-(1-methoxycarbonyl-propylamino)-6-methyl-nicotinic acid methyl ester;

~~SR~~ → ~~✓~~ 3,3',6'-trimethyl-2'-(2,4,6-trimethyl-phenoxy)-3,4,5,6-tetrahydro-2H-[1,4]bipyridinyl;
2-(4-chloro-2,6-dimethyl-phenoxy)-6,N-dimethyl-4-(S)-(tetrahydro-furan-3-ylamino)-nicotinamide; 50-1

10 [7-(4-bromo-2,6-dimethyl-phenyl)-2,5-dimethyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-
(tetrahydro-furan-3-yl)-amine;

15 2,5,6-trimethyl-4-pyrrolidin-1-yl-7-(2,4,6-trimethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidine;
(2-pyrrolidin-1-yl-ethyl)-[2,5,6-trimethyl-7-(2,4,6-trimethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-amine;

20 ~~x~~ 15 (tetrahydro-furan-3-yl)-[2,5,6-trimethyl-7-(2,4,6-trimethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-amine;

~~41~~ 2-(4-chloro-2,6-dimethyl-phenoxy)-6-methyl-4-(tetrahydro-furan-3-ylamino)-pyridine-3-carbaldehyde oxime;

~~outside~~ → ~~search~~ 3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-
(2-pyrrolidin-1-yl-ethyl)-amine; N-[3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-2,2,2-trifluoro-N-(2-pyrrolidin-1-yl-ethyl)-acetamide;

25 20 N2-[3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-N1,N1-dimethyl-butane-1,2-diamine;

2-(4-chloro-2,6-dimethyl-phenoxy)-4-(1-ethyl-2-methylamino-propylamino)-6-methyl-nicotinic acid methyl ester;

30 25 [3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-
(3-methyl-butyl)-(2-pyrrolidin-1-yl-ethyl)-amine;

(3,3-dimethyl-butyl)-[3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-
(2-pyrrolidin-1-yl-ethyl)-amine;

[3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-morpholin-4-yl-amine;

- 4-(1-ethyl-propoxy)-2-(4-methoxy-2-methyl-phenylamino)-6-methyl-nicotinic acid;
2-(4-chloro-2-methyl-phenylamino)-4-(1-ethyl-propoxy)-6-methyl-nicotinic acid;
4-(1-ethyl-propylamino)-6-methyl-2-(2,4,6-trimethyl-pyridin-3-yloxy)-nicotinic acid;
N2-[3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-N1-pyridin-3-ylmethyl-
5 butane-1,2-diamine; --
N2-[3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-N1-thiazol-2-ylmethyl-
butane-1,2-diamine; --
2-(2,4-dimethyl-phenylamino)-4-(1-ethyl-propoxy)-6-methyl-nicotinic acid;
[2-(4-chloro-2-methyl-phenylamino)-4-(1-ethyl-propoxy)-6-methyl-pyridin-3-yl]-
10 methanol;
2-(4-chloro-2,6-dimethyl-phenoxy)-4-(1-hydroxymethyl-propylamino)-6-methyl-
nicotinonitrile;
1-(4-chloro-2-methyl-phenyl)-5-(1-ethyl-propoxy)-7-methyl-1,4-dihydro-2H-3-oxa-1,8-
diaza-naphthalene;
15 4-(1-ethyl-propylamino)-2-methyl-7-(2,4,6-trimethyl-phenyl)-7H-pyrrolo[2,3-
d]pyrimidine-5,6-dione;
4-(1-ethyl-propylamino)-2-methyl-7-(2,4,6-trimethyl-phenyl)-5,7-dihydro-pyrrolo[2,3-
d]pyrimidin-6-one;
4-[3-cyano-4-(1-ethyl-propylamino)-6-methyl-pyridin-2-yloxy]-3-methoxy-benzoic acid;
20 2-(4-chloro-2,6-dimethyl-phenoxy)-4-(1-methoxymethyl-propylamino)-6-methyl-
nicotinamide;
2-(4-chloro-2,6-dimethyl-phenoxy)-4-(1-methoxymethyl-propylamino)-6,N-dimethyl-
nicotinamide;
25 2-(4-chloro-2,6-dimethyl-phenoxy)-N-(1-hydroxymethyl-propyl)-4-(1-hydroxymethyl-
propylamino)-6-methyl-nicotinamide;
and pharmaceutically acceptable salts of the above compounds.

The invention also relates to a pharmaceutical composition for the treatment of (a) a disorder or condition the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitated by CRF, or (b) a disorder or condition selected from inflammatory disorders such as rheumatoid arthritis and osteoarthritis, pain, asthma, psoriasis and allergies; generalized anxiety disorder; panic; phobias, including social phobia, agoraphobia, and specific phobias; obsessive-compulsive disorder; post-traumatic stress disorder; sleep disorders induced by stress; pain perception such as fibromyalgia; mood disorders such as depression, including major depression, single episode depression, recurrent depression, child abuse induced depression, mood disorders associated with premenstrual syndrome, and postpartum depression; dysthemia; bipolar disorders; cyclothymia; chronic

fatigue syndrome; stress-induced headache; cancer; irritable bowel syndrome, Crohn's disease; spastic colon; post operative ileus; ulcer; diarrhea; stress-induced fever; human immunodeficiency virus infections; neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and Huntington's disease; gastrointestinal diseases; eating disorders such as anorexia and bulimia nervosa; hemorrhagic stress; chemical dependencies or addictions, including dependencies or addictions to alcohol, cocaine, heroin, benzodiazapines, or other drugs; drug or alcohol withdrawal symptoms; stress-induced psychotic episodes; euthyroid sick syndrome; syndrome of inappropriate antidiuretic hormone; obesity; infertility; head trauma; spinal cord trauma; ischemic neuronal damage, including cerebral ischemia, for example cerebral hippocampal ischemia; excitotoxic neuronal damage; epilepsy; stroke; immune dysfunctions including stress induced immune dysfunctions, including porcine stress syndrome, bovine shipping fever, equine paroxysmal fibrillation, confinement dysfunction in chicken, sheering stress in sheep, and human-animal interaction stress in dogs; muscular spasms; urinary incontinence; senile dementia of the Alzheimer's type; multiinfarct dementia; amyotrophic lateral sclerosis; hypertension; tachycardia; congestive heart failure; osteoporosis; premature birth; hypoglycemia, and Syndrome X in a mammal, including a human, or bird comprising an amount of a compound of the formula I, II or III, or a pharmaceutically acceptable salt thereof, that is effective in the treatment of such disorder or condition, and a pharmaceutically acceptable carrier.

The invention further includes a method for the treatment of (a) a disorder or condition the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitated by CRF, or (b) a disorder or condition selected from inflammatory disorders such as rheumatoid arthritis and osteoarthritis, pain, asthma, psoriasis and allergies; generalized anxiety disorder; panic; phobias, including social phobia, agoraphobia, and specific phobias; obsessive-compulsive disorder; post-traumatic stress disorder; sleep disorders induced by stress; pain perception such as fibromyalgia; mood disorders such as depression, including major depression, single episode depression, recurrent depression, child abuse induced depression, mood disorders associated with premenstrual syndrome, and postpartum depression; dysthemia; bipolar disorders; cyclothymia; chronic fatigue syndrome; stress-induced headache; cancer; irritable bowel syndrome, Crohn's disease; spastic colon; post operative ileus; ulcer; diarrhea; stress-induced fever; human immunodeficiency virus infections; neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and Huntington's disease; gastrointestinal diseases; eating disorders such as anorexia and bulimia nervosa; hemorrhagic stress; chemical dependencies or addictions, including dependencies or addictions to alcohol, cocaine, heroin, benzodiazapines, or other drugs; drug or alcohol withdrawal symptoms; stress-induced psychotic episodes; euthyroid sick

syndrome; syndrome of inappropriate antidiuretic hormone; obesity; infertility; head trauma; spinal cord trauma; ischemic neuronal damage, including cerebral ischemia, for example cerebral hippocampal ischemia; excitotoxic neuronal damage; epilepsy; stroke; immune dysfunctions including stress induced immune dysfunctions, including porcine stress syndrome,
5 bovine shipping fever, equine paroxysmal fibrillation, confinement dysfunction in chicken, sheering stress in sheep, and human-animal interaction stress in dogs; muscular spasms; urinary incontinence; senile dementia of the Alzheimer's type; multiinfarct dementia; amyotrophic lateral sclerosis; hypertension; tachycardia; congestive heart failure; osteoporosis; premature birth; hypoglycemia, and Syndrome X in a mammal, including a human, or bird
10 comprising administering to a subject in need of said treatment an amount of a compound of the formula I, II or III or a pharmaceutically acceptable salt thereof, that is effective in treating such disorder or condition.

The present invention also provides a pharmaceutical composition for and a method of treating a condition comprising administering a compound of I, II, or III, in an amount effective to treat said condition, wherein said condition is selected from the group consisting of: a) abnormal circadian rhythm; b) depression, further wherein a second compound for treating depression is administered, said second compound for treating depression having an onset of action that is delayed with respect to that of said CRF antagonist; and c) emesis. The aforementioned method can practiced according to the information provided in U.S. Provisional Patent Application No. 60/151,183, filed August 27, 1999, which describes treatment of the aforementioned conditions using CRF antagonists in general and which is incorporated herein by reference in its entirety.

The compounds of formula I, II, and III, described herein can also be used to treat forms of heart failure described in U.S. Serial No. 09/248,073, *supra*, and can be made into pharmaceutical compositions therefore.

Examples of more specific forms or manifestations of abnormal circadian rhythm that can be treated according to the present invention include, but are not limited to, time zone change syndrome resulting, seasonal affective disorder, shift-work sleep disorder, irregular sleep-wake pattern, delayed sleep phase syndrome resulting from said abnormal circadian rhythm, advanced sleep phase syndrome, or non-24 hour sleep wake disorder resulting from said abnormal circadian rhythm. Moreover, the compound of formula I, II, or III can be combined in the method or pharmaceutical composition for treatment of abnormal circadian rhythm with a second compound that is useful for treating a sleep disorder, for example tachykinin antagonists, agonists for GABA brain receptors, metalonergic compounds, GABA
30 brain receptor agonists, 5HT₂ receptor antagonists, and D4 receptor binding compounds.
35 However, other compounds or substances useful for treating a sleep disorder can be

combined with a compound of formula I, II, or III. Such methods and compositions are described in greater detail in U.S. Provisional Patent Application No. 60/151,183, *supra*.

In another embodiment, said condition is depression, and the second compound having delayed action for treating depression is selected from the group consisting of 5 selective serotonin reuptake inhibitors, tricyclic antidepressants, norepinephrine uptake inhibitors, lithium, bupropion, sertraline, fluoxetine, trazodone, and a tricyclic antidepressant selected from the group consisting of imipramine, amitriptyline, trimipramine, doxepin, desipramine, nortriptyline, protriptyline, amoxapine, clomipramine, maprotiline, and carbamazepine, and pharmaceutically acceptable salts and esters of the above-recited 10 compounds.

In another embodiment, the condition being treated is emesis, and the method further comprises administering a second compound for treating emesis. The second compound for treating emesis can be selected from, but is not limited to, tachykinin antagonists, 5HT3 antagonists, GABA agonists, and substance P inhibitors. More specific categories of emesis 15 encompassed in the present invention include emesis induced by a condition or agent selected from the group consisting of pregnancy, vestibular disorder, post-operative sickness, gastrointestinal obstruction, reduced gastrointestinal motility, visceral pain, migraine, change in intracranial pressure, chemotherapy, radiation, toxins, and opioid analgesics.

Detailed Description of the Invention

20 Methods of preparing the compounds and compositions of this invention are described below. In the discussion and reaction schemes that follow, R₁ through R₉, R₁₁, R₁₂, R₁₆, R₁₇, R₁₉, A, B, G, the dashed lines and structural formulae I, II, III, X, XI, XII and IV, unless otherwise indicated, are defined as above.

25 Whenever reference is made herein to alkyl, both straight and branched chain alkyl groups are encompassed. For example, "C₁-C₆ alkyl" encompasses both straight and branched chain alkyl groups of one to six carbon atoms, including (but not limited to) methyl, ethyl, isopropyl, t-butyl and hexyl.

Whenever R₂ or R₅ is a heterocyclic group, attachment of the group is through a carbon atom.

30 Whenever reference is made herein to C₁-C₄ alkyl or C₁-C₆ alkyl which "may contain one double or triple bond" in the above definitions, it is understood that at least two carbons are present in the alkyl for one double or triple bond.

Whenever reference is made herein to halo or halogen; fluoro, chloro, bromo or iodo is meant unless indicated otherwise.

35 The terms "treatment", "treating", and the like, are meant to include both slowing or reversing the progression of a disorder, as well as curing the disorder. These terms also

include alleviating or reducing the symptoms of a disorder or condition, even if the disorder or condition is not actually eliminated and even if progression of the disorder or condition is not itself slowed or reversed. The term "treatment" and like terms also include prophylactic treatment of disorders and conditions.

5 The term "haloalkyl" refers to an alkyl group substituted by one or more halogen atoms, i.e. one or more fluoro, bromo, iodo, or chloro atoms. Moreover, it is understood that when an alkyl group can be, according to this specification and claims, substituted with, e.g., one to nine, e.g., nine atoms, that the optional one to nine fluorine atoms are only an option when a sufficient number of carbon atoms is present in the alkyl group.

10 The term "aryl" in the definitions above means, unless otherwise indicated, an organic radical derived from an aromatic hydrocarbon by removal of one hydrogen atom. Examples of aryl groups are phenyl and naphthyl.

The term "heterocycloalkyl", unless otherwise specified means a 4 to 8 membered mono-carbocyclic ring or bicyclic ring, wherein at least one carbon atom is replaced with a 15 hetero member selected from oxygen, nitrogen, N-(alkyl), or S(O)_m, wherein m is zero, 1, 2, or 3. Generally, heterocycloalkyl groups comprise up to four hetero members, preferably 1, 2, or 3 hetero members. Heterocycloalkyl groups of the compounds of the invention can contain optionally from one to three double bonds. The term "heterocycloalkyl" also includes heteroaryl groups. Examples of heteroaryl groups include thieryl, benzothienyl, pyridyl, 20 thiazolyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, benzisoxazolyl, benzimidazolyl, indolyl, and benzoxazolyl. Other examples of aryl groups are pyrazolyl, triazolyl, tetrazolyl, isoxazolyl, oxazolyl, pyrrolyl, isoquinolinyl, cinnolinyl, indazolyl, indolizinyl, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, purinyl, oxadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzothiazolyl, 25 benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, and furopyridinyl. Preferred heteroaryl groups are thiazolyl, thieryl, benzothienyl, pyridyl, quinolyl, quinazolinyl, quinoxalinyl, pyrazinyl, pyrimidinyl, indazolyl, imidazolyl, furanyl, benzimidazolyl, benzofuranyl, benzothiazolyl, benzisoxazolyl, isothiazolyl, pyrazolyl, pyrrolyl, indolyl, pyrrolopyridyl, oxazolyl, benzoxazolyl, and benzothiadiazolyl. Other preferred heterocycloalkyl groups are tetrahydrofuran, 30 tetrahydropyran, morpholino, pyrrolidino, piperidino, piperazine, [2,2,1]-azabicyclic rings, [2,2,2]-azabicyclic rings, [3,3,1]azabicyclic rings, quinuclidino, azetidino, azetidinono, oxindolo, dihydroimidazolo, and pyrrolidinono. Heterocyclolalkyl groups in the compounds of the invention may be C-attached or N-attached where such is possible.

Compounds of the formula I wherein B is -NR₁R₂, -NHCHR₁R₂, -OCHR₁R₂ or 35 -SCHR₁R₂, and R₃ is methyl, ethyl or chloro (hereinafter R₁₉) may be prepared by reaction of a compound of the formula IV wherein D is Cl, and A, R₄, R₅, and Z are as defined above with

reference to formula I, with a compound of the formula BH wherein B is as defined immediately above. The reaction is carried out in a solvent in the presence of a base at a temperature of between about 0° to about 230°C. Suitable solvents are organic solvents such as tetrahydrofuran (THF), acetonitrile, dimethylsulfoxide (DMSO), acetone, C₂-C₁₅ alkyl alcohol, 5 chloroform (CHCl₃), benzene, xylene, toluene, sulfolane, pyridine, quinoline, 2,4,6-trimethylpyridine, acetamide, di-(C₁-C₂)alkylacetamide or 1-methyl-2-pyrrolidinone.

A preferred method of preparing compounds of the formula I wherein A is -CR₇ and B is -NR₁R₂ or -NHCHR₁R₂ is the two step procedure described below. First, a compound of the formula IV is reacted with an excess of R₁NH₂ or NH₃ or an equivalent NH₃ precursor (e.g., 10 NaN₃, nBu₄N⁺N₃⁻ or NH₂OH) at temperature from about 75°C to about 250°C and at a pressure from about 0 to about 300 psi, in an appropriate solvent, as described above, to form a compound of the formula I wherein B is -NHR₁, -NH₂, -NH₂OH or -N₃. Compounds of the formula I wherein B is -N₃ or -NH₂OH can be converted into the corresponding compounds of formula I wherein B is -NH₂ by methods well known in the art such as hydrogenation or 15 reduction. Alkylation of a compound of the formula I wherein B is -NHR₁ or -NH₂ with an appropriate alkyl halide in the presence of an appropriate base such as lithium or sodium bistrimethylsilylamine, lithium or sodium diisopropylamide, n-butyllithium or potassium t-butoxide, in an appropriate solvent such as THF, dioxane or methylene chloride, will yield the corresponding compound of formula I wherein B is -NR₁R₂. Alternatively, reductive amination of 20 a compound of the formula I wherein B is -NHR₁ or -NH₂, for example, acylation, followed by reduction with a borohydride (e.g., sodium borohydride) will form the corresponding compound of formula I wherein B is -NR₁R₂ or NHCHR₁R₂.

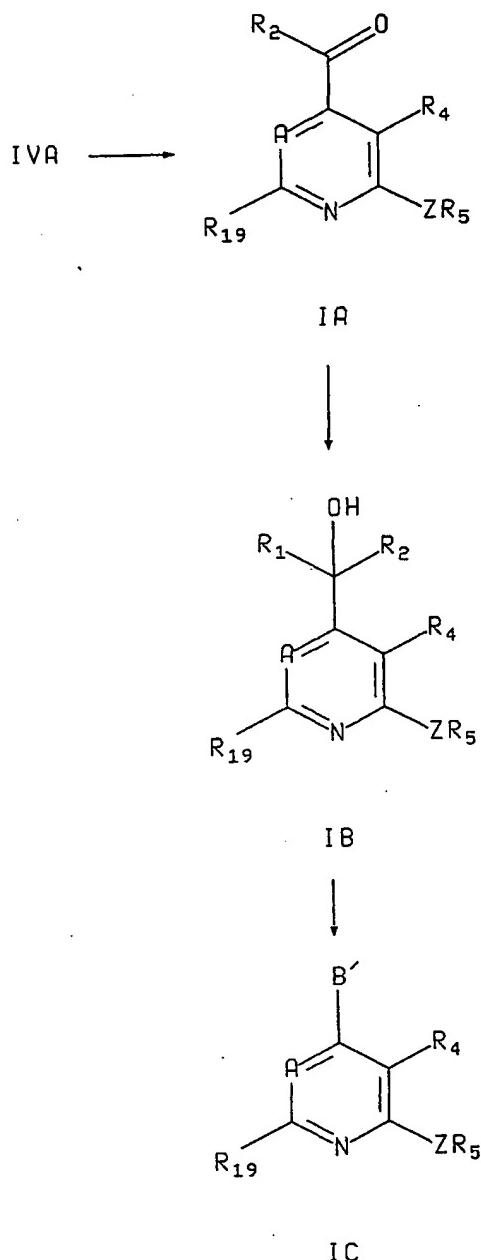
When B is -NR₁R₂ or -NHCHR₁R₂, an excess of BH may be used both as a reagent and as a base. Bases other than BH such as potassium carbonate, tri-(C₁-C₆)alkylamine or 25 sodium hydride may also be used. The reaction is carried out at a temperature of about 75° to 230°C. When the reaction is carried out in the presence of a base, such as sodium hydride, potassium C₁-C₄ alkoxide, or an organolithium compound such as n-butyllithium, a molar equivalent of the amine is used.

When B is -OCHR₁R₂ or -SCHR₁R₂, a base which is capable of deprotonating BH may 30 be used, such as an alkali metal hydride such as sodium or potassium hydride, or an organometallic base such as sodium diisopropylamide, sodium bis(trimethylsilyl)amide, lithium diisopropylamide, lithium bis(trimethylsilyl)amide, sodium or potassium C₁-C₄ alkoxide, or n-butyllithium. The solvent used can be, for example, tetrahydrofuran, acetonitrile, dimethylsulfoxide, acetone, methylene chloride, toluene, a C₂-C₅ alcohol, chloroform, benzene, 35 xylene, or 1-methyl-2-pyrrolidinone, and the reaction temperature can range from about 0°C to about 180°C, and is preferably from about 50°C to about 80°C.

Compounds of the formulae I, II and III wherein B is as defined with reference to formulae I, II and III and R₃ is defined with reference to the same except that R₃ is not methyl or ethyl (hereinafter R₂₀, which is defined as R₃ with the exception that it can not be methyl or ethyl) may be prepared by reacting a compound of the formulae I, II or III wherein R₃ is chloro with a nucleophile of the formula R₂₀H with or without an organic or inorganic base. Suitable bases include sodium and sodium hydride, when R₂₀H is an alkanol or an alkane thiol; and weaker bases such as potassium carbonate or triethylamine when R₂₀H is an amine. The compounds of formula I wherein R₂₀ is fluoro may be prepared from the corresponding compounds wherein R₂₀ is chloro on reaction with tetrabutylammonium fluoride. Suitable solvents are dimethylsulfoxide, tetrahydrofuran, or methylene chloride, preferably tetrahydrofuran.

Compounds of the formula I wherein B is -CR₁R₂R₁₁, -C(C=CR₂R₁₂)R₁, -CHR₂OR₁₂, -CHR₂SR₁₂, or -C(O)R₂, and R₃ is R₁₉, as defined above, may be prepared as depicted in Scheme I.

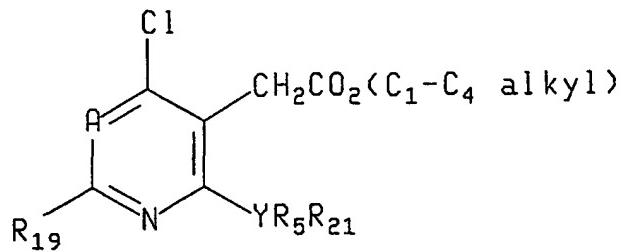
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SCHEME 1

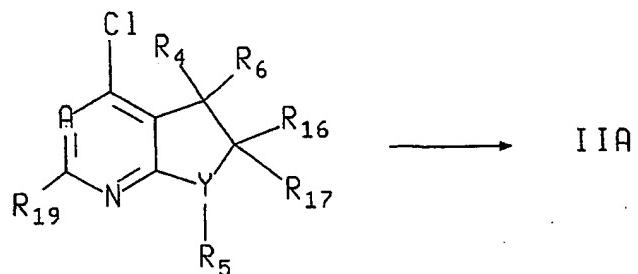
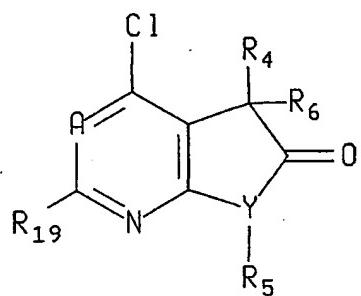
Compounds of the formula IV wherein D is cyano and A, R₄, R₅, and R₁₉ are as defined above having formula IVA (not shown), prepared by reacting the corresponding compound wherein D is chloro with potassium cyanide or copper cyanide in dimethylsulfoxide, 1-methyl-2-pyrrolidinone, N,N-dimethylformamide (DMF) or acetamide, are reacted with a Grignard reagent containing group R₂, as defined above, to form the compounds of formula IA. Further reaction of the compound of formula IA with a Grignard reagent containing R₁ as defined above provides the compound of formula IB. Corresponding compounds of formula IC wherein B" is -CR₁R₂R₁₁, or -C(C=CR₂R₁₂)R₁ may be prepared by conventional methods. Thus, reaction of IB with an acid, such as concentrated sulfuric acid in acetic acid, or Burgess inner salt, such as (carboxysulfamoyl)triethylammonium hydroxide methyl ester, gives a compound of formula IC wherein B' is -C(=CR₂R₁₂)R₁. Hydrogenation of a compound wherein B' is -C(=CR₂R₁₂)R₁ using a palladium/carbon (Pd/C) or platinum dioxide catalyst gives a compound IC wherein B' is CHR₁R₂. Reaction of compound IB with diethylaminosulfur trifluoride or triphenylphosphine/carbontetrachloride affords a compound IC wherein B' is -CR₁R₂F or -CR₁R₂Cl, respectively. Reduction of a compound of formula IA with sodium borohydride gives a compound I wherein B is -CHR₂OH. Alkylation of this -CHR₂OH group with alkyl halide such as alkyl iodide in the presence of a base such as sodium hydride at room temperature affords a compound of formula I wherein B is -CHR₂OR₁₂.

Compounds of the formula II wherein R₃ is R₁₉ as defined above may be prepared from compounds of the formula IV wherein R₁₉, R₄, R₅ and A are as defined before, D is chloro, and YR₂₁ is NH or -CHR₂₁ wherein R₂₁ is cyano or -COO(C₁-C₄ alkyl), hereafter formula IVB, as shown in Scheme 2.

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SCHEME 2

IVB



IIIA

Compounds of the formula VII wherein R₄ and R₆ are each hydrogen and Y is N may be prepared by heating compounds of formula IVB with an acid catalyst in a suitable solvent such as toluene, benzene, t-butanol, acetonitrile and acetone, preferably toluene. The acid catalyst may be sulfuric acid, hydrochloric acid, p-toluene sulfonic acid, or methylsulfonic acid, 5 preferably p-toluene sulfonic acid.

When Y in formula IVB is CH or N, a base may be used to deprotonate the proton of the compound of formula IVB. Suitable solvents are tetrahydrofuran, toluene, and methylene chloride, suitable reaction temperatures are between about -78°C and 100°C, preferably -78° to 10 50°C, and suitable bases are sodium hydride, potassium hydride, potassium t-butoxide, lithium bis(trimethylsilyl) amide, and lithium or sodium diisopropylamide.

Compounds of the formula VII wherein R₄ and R₆ are each hydrogen may be deprotonated with a base such as sodium hydride, or an organometallic compound such as lithium bis(trimethylsilyl)amide followed by quenching with an electrophile compound containing the group R₄, such as R₄L wherein L is a leaving group such as iodo, bromo, mesylate, tosylate 15 or with p-tolyl-N-fluoro-N-C₁-C₆ alkyl sulfonamide, iodine, p-nitrobenzene, dimethylformamide, di(C₁-C₄ alkyl)ketone, formaldehyde, (C₁-C₄ alkyl) aldehyde or bromine, to provide a compound of formula VII wherein R₄ is fluoro, chloro, bromo, iodo, hydroxy, C₁-C₄ alkyl, S(C₁-C₄ alkyl), CHO, CH(OH)(C₁-C₄ alkyl), C(OH)(di-C₁-C₄ alkyl) or CH₂OH. Further conventional alkylation of the hydroxy group or oxidation of the thioalkyl group leads to compounds of formula VII wherein 20 R₄ is C₁-C₄ alkoxy and SO_n(C₁-C₄ alkyl) wherein n is 1 or 2, respectively. Oxidation of compounds of formula VII wherein R₄ is hydroxy and R₆ is hydrogen affords corresponding compounds wherein CR₄R₆ is C=O, which on reductive amination with an appropriate amine convert into corresponding compounds wherein R₄ is amino. The compounds of formula VII wherein R₄ is nitro or amino may be formed by reacting compounds of formula VII wherein R₄ 25 and R₆ are both hydrogen with alkyl nitrite to form compounds wherein CR₄R₆ is C=NOH and oxidizing or reducing to give the compounds of formula VII wherein R₄ is nitro or amine, respectively.

Compounds of the formula VII, when one of R₄ and R₆ is hydrogen, may be converted into corresponding compounds wherein R₁₆ and R₁₇ are both hydrogen by reduction with a 30 reducing agent such as lithium aluminum hydride in tetrahydrofuran. The same reduction leads to compounds wherein R₁₆ is hydrogen and R₁₇ is hydroxy, when both of R₄ and R₆ are not hydrogen. Alkylation when R₁₇ is hydroxy with C₁-C₄ alkyl iodide in the presence of sodium hydride gives the corresponding compound wherein R₁₇ is O(C₁-C₄ alkyl). Reaction of compounds of formula VII with an organometallic compound such as di(C₁-C₆ alkyl)zinc, C₁-C₆ 35 alkyl lithium, or C₁-C₆ alkyl magnesiumbromide affords compounds of formula VIII wherein one of R₁₆ or R₁₇ is C₁-C₆ alkyl and the other is hydroxy.

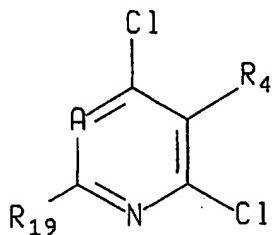
The conversion of compounds of formula VIII to corresponding compounds of formula IIA is by the methods described above for preparation of compounds of formula I.

The compounds of formula III wherein G is oxygen or sulfur and R₆ is hydrogen may be prepared by reacting compounds of formula I wherein R₄ is amino and Z is NH with phosgene, diphosgene, triphosgene or thiophosgene. The reaction is in the presence of a base such as tri(C₁-C₄ alkyl)amine in a suitable solvent, preferable tetrahydrofuran at about -78° to about 50°C, preferably at 0°C to room temperature. Standard alkylation of these compounds wherein R₆ is hydrogen with a suitable base such as sodium hydride in a suitable solvent such as dry tetrahydrofuran provides compounds of the formula III wherein R₆ is C₁-C₄ alkyl.

Compounds of the formula III wherein G is alkyl may be prepared by reacting a compound of the formula I wherein R₄ is amino and Z is NH with a compound of the formula GC(OC₁-C₂ alkyl)₃ in the presence of an acid such as p-toluenesulfonic acid (p-TsOH), methanesulfonic acid (MsOH), hydrogen chloride gas (HCl_g) or concentrated sulfuric acid (H₂SO₄) in an appropriate solvent such as toluene, xylene, benzene, dioxane or THF at a temperature from about room temperature to about 140°C, preferably from about 50°C to about the reflux temperature. Alternatively, a compound of the formula I wherein R₄ is amino and Z is NH can be reacted with [G(C=O)]₂O, G(C=O)Cl or G(C=O)F in the presence of a base such as pyridine, a derivative of pyridine or a tri-(C₁-C₄)alkylamine, in an appropriate solvent such as CH₂Cl₂, CHCl₃, THF, dioxane, toluene or benzene, at a temperature from about 0°C to about the reflux temperature of the reaction mixture, preferably from about 0°C to about room temperature, followed by ring cyclization under acidic conditions (e.g., with pTSOH, MSOH, HCl_g, hydrogen bromide gas (HBr_g) or concentrated H₂SO₄). The ring cyclization can be carried out in an appropriate solvent such as a C₁-C₅ alcohol, toluene, xylene, benzene, dioxane or THF. Suitable temperatures for this reaction can range from about room temperature to about 140°C. Preferably, the reaction temperature is between about 50°C and about the reflux temperature.

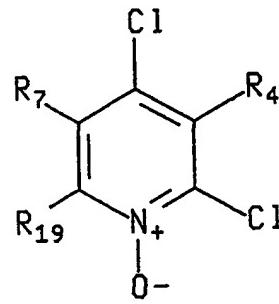
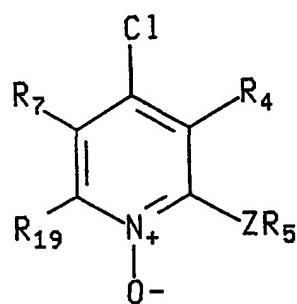
Compounds of the formula III wherein G is -O-(C₁-C₂ alkyl) or -OCF₃ may be prepared by reacting a compound of the formula III wherein G is oxygen and R₆ is hydrogen with a compound of the formula GOSO₂CF₃ in the presence of a base such as tri(C₁-C₄ alkyl)amine, or with lithium bistrimethylsilyl amide in HMPA or DMF, and then quenching the reaction with a compound of the formula GOSO₂OG or G-X wherein X is bromo, chloro or SO₃CF₃.

The compounds of formula IV wherein D is chloro and ZR₅ is NHR₅ may be prepared from compounds of formula V:



- wherein A and R₄ are as defined with reference to formula I and R₁₉ is as defined above, by reaction with R₅NH₂. The reaction is in tetrahydrofuran or dimethylsulfoxide at about 0°C to about 150°C, preferably 50° to 130°C. The compounds of formula IV wherein D is chloro and
- 5 Z is O, S, CHR₂₁ wherein R₂₁ is an electron deficient group such as cyano, C(=O)R, COOR, wherein R is C₁-C₄ alkyl, benzoyl or allyl, or SO_n- phenyl wherein n = 0, 1 or 2 may be prepared by reacting compounds of formula V with R₅OH, R₅SH, R₅NH₂ or R₅CHR₂₁. The reaction proceeds in the presence of a base which is capable of deprotonating R₅ZH, such as sodium hydride, potassium hydride, potassium carbonate, lithium or sodium
- 10 bis(trimethylsilyl)amide, lithium or sodium dialkylamide, sodium or potassium (C₁-C₄ alkoxide) or n-butyllithium, with or without other organometal halides such as copper (I) bromide, iodide or chloride, copper (II) oxide, copper (I) oxide, copper metal and trialkyltinchloride. Examples of solvents that may be used are tetrahydrofuran, dimethylsulfoxide, acetonitrile, methylene chloride, 1-methyl-2-pyrrolidinone, pyridine, quinoline, N,N-dialkylacetamides, 2,4,6-
- 15 trimethylpyridine, N,N-dialkylformamides, e.g., N,N-dimethylformamide (DMF), hexamethyl phosphoramide and toluene. The reaction temperature may range from about 0°C to about 180°C, and is preferably from about 0° to about 150°C.

Compounds of the formula IV wherein A is CR₇, D is chloro and Z is O, S, CHR₂₁ may be prepared by reduction of compounds of formula X, depicted below, wherein R₇ and Z are as defined immediately above, with a reducing agent such as phosphorous trichloride in an appropriate solvent such as methylene chloride or chloroform at temperature from about 0°C to about 100°C, preferably from about room temperature to about the reflux temperature of the solvent.



Compounds of the formula X may be prepared from compounds of the formula XI, depicted above, wherein R₄ is as defined as it is for formula I and R₁₉ is as defined above (i.e., methyl or ethyl), by reaction with a compound of the formula R₅OH, R₅SH or R₅CHR₂₁. This reaction 5 proceeds in the presence of a base which is capable of deprotonating R₅ZH, such as sodium hydride, potassium hydride, lithium, sodium or potassium bis(trimethylsilyl)amide, lithium, sodium or potassium dialkylamide, sodium or potassium C₁-C₄alkoxide, or n-butyllithium. Suitable solvents include tetrahydrofuran, dioxane, dimethylsulfoxide, 1-methyl-2-pyrrolidinone, pyridine, N,N-di-(C₁-C₄ alkyl)acetamides, acetamide, N,N-di-(C₁-C₄ alkyl)formamides, acetonitrile, methylene chloride, toluene and xylene. Suitable reaction 10 temperatures may range from about -78°C to about 150°C, and are preferably between about -40°C to about 150°C.

Compounds of the formula XI may be prepared by reacting the corresponding compounds of formula V wherein A is -CR₇ and R₄ and R₁₉ are defined as above, with an 15 oxidizing agent such as m-chloroperbenzoic acid, peracetic acid or pertrifluoroacetic acid, in a solvent such as methylene chloride, chloroform, acetic acid, DMF, methanol or a mixture of one or more of the foregoing solvents, at temperature from about 0°C to about 100°C, preferably from about room temperature to about 60°C.

When R₄ is an electron withdrawing group such as a NO₂, -COO(C₁-C₄ alkyl), -COOH, 20 CN or -CO(C₁-C₄)alkyl, the reaction order for the coupling reactions that introduce the B and ZR₅ groups in the synthesis of compounds of formula I may be reversed. The B group may be introduced before the ZR₅ coupling step using the methods analogous to those described above. For example, compounds of the formula I wherein R₄ is an election deficient group may be prepared by reacting a compound of the formula XII with a compound of the formula HZR₅. 25 Compounds of the formula XII may be prepared by reacting a compound of the formula V

wherein A is CR₇ and R₁₉ and R₄ are defined as above with a compound of the formula B''H in the presence of a base.

Compounds of the formula IV wherein D is chloro and Z is -N(C₁-C₄ alkyl) may be prepared by reacting the corresponding compounds wherein Z is NH with a base, at a temperature from about -78°C to about 100°C, preferably from about 0°C to about room temperature, followed by quenching with C₁-C₄ alkyl iodide or bromide. Suitable bases include, for example, sodium hydride, lithium or sodium bis(trimethylsilyl)amide, lithium or sodium dialkylamide, and n-butyllithium. Suitable solvents include, for example, tetrahydrofuran, dimethylsulfoxide, toluene or methylene chloride.

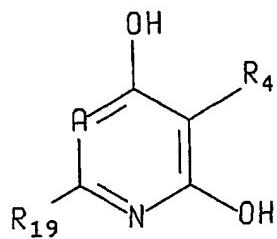
- 10 Compounds of the formula IV wherein D is chloro, hydroxy or OP wherein P is a standard protecting group for hydroxy and Z is -CR₁₃R₁₄ may be prepared by alkylation, using an R₁₃ containing alkylating agent such as R₁₃I, compounds of the formula IV wherein Z is -CHR₂₁ in the presence of a base that is capable of deprotonating the proton in the Z group, as mentioned above, followed by quenching with an R₁₄ containing alkylating agent such as R₁₄I.
- 15 Heating compounds of the formula IV wherein D is chloro or hydrogen and Z is -CH(CN) in about 85% phosphoric acid at about the reflux temperature yields the corresponding compounds of formula IV wherein D is hydroxy and Z is CH₂. Deprotonation of the compounds of formula IV wherein Z is CH₂ with a base, such as described above for deprotonation of R₅ZH, followed by quenching with a suitable electrophile such as a (C₁-C₆ alkyl)iodide, iodine, bromine, acetylchloride, formaldehyde, acetone, p-tolyl-N-fluoro-N-(C₁-C₆ alkyl)sulfonamide, nitrobenzene, C₁-C₆ alkynitrite, ethylene oxide or dihaloethane yields the corresponding compounds of formula IV wherein Z is -CHR₁₃, -CH(OH), cyclopropyl or -C(NOH). Further alkylation of compounds wherein Z is -CHR₁₃, e.g., as described immediately above, with an alkylating agent of the formula R₁₄I, produces the corresponding compounds wherein Z is -C(R₁₃R₁₄).

Conversion of -C(R₅)NOH or -CH(OH)R₅ to C(O)R₅ may be accomplished by known methods. Hydrogenation or reduction of compounds wherein Z is -C=NOH provides compounds wherein Z is -CHNH₂. Some of the intermediates may require a protecting or deprotecting procedure to control the reaction selectivity using standard organic chemistry.

- 30 Compounds of the formula V wherein A is N (hereinafter referred to as compounds of the formula VB) or A is CR₇ (i.e., compounds of the formula VA), and R₄ and R₁₉ are defined as they are for formula I, may be prepared by reacting the corresponding compounds of formulae VIB and VIA, respectively, with 1 equivalent or an excess of POCl₃ at a temperature from about room temperature to about 180°C, preferably at the reflux temperature, with or without a solvent. Compounds of formula VIA may be prepared by the methods analogous to those

described in the literature and well known to those skilled in the art. (See Helv. Chimica Acta., 25, p. 1306-1313 (1942)).

Compounds of formula VI B may be prepared by reacting 1 equivalent of the HCl salt of R₁₉C(=NH)(NH₂), 1 equivalent of R₄CH(COO-(C₁-C₂ alkyl))₂, and 2 equivalents of a base such 5 as a sodium alkoxide, e.g., sodium methoxide in a mixture of an alcohol (e.g., methanol), and acetone at a temperature from about 50°C to about 200°C, preferably at the reflux temperature.



VIA, A = CR₇

VI B, A = N

When compounds of this invention contain one or more chiral centers, it is understood that the invention includes the racemic mixtures as well as all individual enantiomers and 10 diastereomers of such compounds, and mixtures thereof.

The subject invention also includes isotopically-labeled compounds, which are identical to those recited in formulas I, II, or III, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into 15 compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, iodine, and chlorine, such as ³H, ¹¹C, ¹⁴C, ¹⁸F, ¹²³I and ¹²⁵I. Compounds of the present invention and pharmaceutically acceptable salts of said 20 compounds that contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Isotopically-labeled compounds of the present invention, for example those into which radioactive isotopes such as ³H and ¹⁴C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ³H, and carbon-14, i.e., ¹⁴C, isotopes are particularly preferred for their ease of preparation and detectability. ¹¹C and ¹⁸F isotopes are particularly useful in PET (positron emission tomography), and ¹²⁵I isotopes are particularly useful in SPECT (single photon emission computerized tomography), all useful in brain imaging. Further, substitution with heavier 25 isotopes such as deuterium, i.e., ²H, can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically labeled

compounds of formulas I, II, or III of this invention can generally be prepared by carrying out the procedures disclosed in the Schemes and/or in the Examples below, by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent.

The acid addition salts of compounds of the formulae I, II and III ("the active compounds of this invention) can be prepared in a conventional manner by treating a solution or suspension of the corresponding free base with one chemical equivalent of a pharmaceutically acceptable acid. Conventional concentration or crystallization techniques can be employed to isolate the salts. Illustrative of suitable acids are acetic, lactic, succinic, maleic, tartaric, citric, gluconic, ascorbic, benzoic, cinnamic, fumaric, sulfuric, phosphoric, hydrochloric, hydrobromic, hydroiodic, sulfamic, sulfonic acids such as methanesulfonic, benzene sulfonic, p-toluenesulfonic, and related acids.

The active compounds of this invention may be administered alone or in combination with pharmaceutically acceptable carriers, in either single or multiple doses. Suitable pharmaceutical carriers include inert solid diluents or fillers, sterile aqueous solutions and various organic solvents. The pharmaceutical compositions formed by combining the novel compounds of formulae I, II and III and their pharmaceutically acceptable carriers can then be readily administered in a variety of dosage forms such as tablets, powders, lozenges, syrups, injectable solutions and the like. These pharmaceutical compositions can, if desired, contain additional ingredients such as flavorings, binders, excipients and the like. Thus, for purposes of oral administration, tablets containing various excipients such as sodium citrate, calcium carbonate and calcium phosphate may be employed along with various disintegrants such as starch, methylcellulose, alginic acid and certain complex silicates, together with binding agents such as polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often useful for tabletting purposes. Solid compositions of a similar type may also be employed as fillers in soft and hard filled gelatin capsules. Preferred materials for this include lactose or milk sugar and high molecular weight polyethylene glycols. When aqueous suspensions or elixirs are desired for oral administration, the essential active ingredient therein may be combined with various sweetening or flavoring agents, coloring matter or dyes and, if desired, emulsifying or suspending agents, together with diluents such as water, ethanol, propylene glycol, glycerin and combinations thereof.

For parenteral administration, solutions containing an active compound of this invention or a pharmaceutically acceptable salt thereof in sesame or peanut oil, aqueous propylene glycol, or in sterile aqueous solution may be employed. Such aqueous solutions should be suitably buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. These particular aqueous solutions are especially suitable for intravenous,

intramuscular, subcutaneous and intraperitoneal administration. The sterile aqueous media employed are all readily available by standard techniques known to those skilled in the art.

The effective dosages for compounds of the formulae I, II or III and their salts will depend on the intended route of administration and factors such as the age and weight of the patient, as generally known to a physician. The dosages will also depend on the particular illness to be treated. For instance, the daily dosage for stress-induced illnesses, inflammatory disorders, Alzheimer's disease, gastro-intestinal diseases, anorexia nervosa, hemorrhagic stress and drug and alcohol withdrawal symptoms will generally range from about 0.1 to about 50 mg/kg body weight of the patient to be treated. The effective dose can be determined by those of ordinary skill in the art by reference to texts pertaining to treatment of the particular disorder or condition to be treated.

Methods that may be used to determine the CRF antagonist activity of the active compounds of this invention and their pharmaceutically acceptable salts are described in Endocrinology, 116, 1653-1659 (1985) and Peptides, 10, 179-188 (1985). The binding activities for compounds of formulae I, II and III, expressed as IC₅₀ values, generally range from about 0.5 nanomolar to about 10 micromolar.

The present invention is illustrated by the following examples. It will be understood, however, that the invention is not limited to the specific details of these examples. Melting points are uncorrected. Proton nuclear magnetic resonance spectra (¹H NMR) and C¹³ nuclear magnetic resonance spectra (C¹³ NMR) were measured for solutions in deuteriochloroform (CDCl₃) and peak positions are expressed in parts per million (ppm) downfield from tetramethylsilane (TMS). The peak shapes are denoted as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad.

The following abbreviations are used in the Examples: Ph=phenyl; iPr=isopropyl; HRMS=high resolution mass spectrum.

Example 1

The compounds below were prepared by reaction of (2-chloro-6-methyl-3-nitro-pyridin-4-yl)-(alkyl- or dialkyl)-amine with substituted phenol by a method analogous to the following: To a mixture of (2-chloro-6-methyl-3-nitro-pyridin-4-yl)-(alkyl- or dialkyl)-amine (1 mmol) and 2,4,6-trimethylphenol (1 mmol) in dry THF was added potassium tert-butoxide (1 mmol) and the resulting mixture was stirred at room temperature until all starting material was consumed. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was dried and concentrated to give the title compound after purification through silica gel column chromatography:

- 2-[2-(4-Chloro-2,6-dimethyl-phenoxy)-6-methyl-3-nitro-pyridin-4-(S)-ylamino]-butan-1-ol
- 1H NMR(CDCl₃) d 7.69(1H), 6.289s, 1H), 3.65-3.80(m, 2H), 3.60m, 1H), 2.12(s, 3H), 2.08(s, 6H), 1.8(brs, 1H), 1.5-1.8(m, 2H), 1.01(t, 3H) ppm.
- 5 (1-Methoxymethyl-propyl)-[6-methyl-3-nitro-2-(4-trifluoromethoxy-phenoxy)-pyridin-4-yl]-amine
- yellow solid, mp. 75-76 °C, Anal. For C₁₈H₂₀N₃O₅F₃, calc. C52.05; H, 4.85; N, 10.12; found, C, 52.14; H, 5.04; N, 10.13
- 10 2-(2-Amino-4,6-dichloro-phenoxy)-6-methyl-3-nitro-pyridin-4-yl]-[1-methoxymethyl-propyl]-amine
- 1H NMR (CDCl₃) d 9.55(d, 1H), 7.23(d, 1H), 7.00(d, 1H), 6.05(s, 1H), 3.69(m, 1H), 3.49(m, 2H), 3.38(s, 3H), 2.35(s, 3H), 1.78(m, 1H), 1.65(m, 1H), 0.99(t, 3H) ppm.
- 15 3-Methoxy-2-[4-(1-methoxymethyl-propylamino)-6-methyl-3-nitro-pyridin-2-yloxy]-benzaldehyde
- yellow solid, mp. 126.5-130.5°C, Anal. For C₁₉H₂₃N₃O₆, calc. C58.60; H, 5.95; N, 10.79; found, C, 58.45; H, 6.11; N, 10.32
- 20 [2-(2,6-Dibromo-4-trifluoromethoxy-phenoxy)-6-methyl-3-nitro-pyridin-4-yl]-[1-methoxymethyl-propyl]-amine
- yellow solid, 1H NMR(CDCl₃) d 8.00(d, 1H), 7.49(2H), 6.35(s, 1H), 3.64(m, 1H), 3.53(m, 2H), 3.43(s, 3H), 2.20(s, 3H), 1.6-1.9(m, 4H), 1.04(t, 3H) ppm.
- 25 [2-(2-Bromo-4-chloro-6-methoxy-phenoxy)-6-methyl-3-nitro-pyridin-4-yl]-[1-methoxymethyl-propyl]-amine
- yellow solid, mp. 111.8-113.6°C, Anal. For C₁₅H₂₁N₃O₅BrCl, calc, C, 45.54; H, 4.46; N, 8.85; found, C, 45.94; H, 4.32; N, 8.68
- 30 [2-(2,4-Dichloro-phenoxy)-6-methyl-3-nitro-pyridin-4-yl]-[1-methoxymethyl-propyl]-amine
- 1H NMR (CDCl₃) d 7.83(d, 1H), 7.46(d, 1H), 7.30(dd, 1H), 7.15(dd, 1H), 6.33(s, 1H), 3.65(m, 1H), 3.51(m, 2H), 3.42(s, 3H), 2.21(s, 3H), 1.82(m, 1H), 1.66(m, 1H), 1.03(t, 3H) ppm.
- 35 [2-(2-Bromo-6-chloro-4-methoxy-phenoxy)-6-methyl-3-nitro-pyridin-4-yl]-[1-methoxymethyl-propyl]-amine
- 1H NMR(CDCl₃) d 7.88(d, 1H), 7.04(d, 1H), 6.93(d, 1H), 6.27(s, 1H), 3.79(s, 3H), 3.60(m, 1H), 3.4-3.5(m, 2H), 3.38(s, 3H), 2.15(s, 3H), 1.78(m, 1H), 1.64(m, 1H), 0.99(t, 3H)
- (1-Methoxymethyl-propyl)-[6-methyl-3-nitro-2-(2,4,6-trimethoxy-phenoxy)-pyridin-4-yl]-amine
- mp. 126.8-129.5°C; Anal. For C₂₀H₂₇N₃O₇ calc. C, 57.00; H, 6.46; N, 9.97; found C, 56.94; H, 6.85; N, 9.66.

Example 22-Chloro-N-[4-(1-ethyl-propylamino)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-3-yl]-acetamide

To a solution of N-4-(1-ethyl-propyl)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridine-3,4-diamine (250 mg, 0.763 mmol) in dry THF was added chloroacetyl chloride (86 mg, 0.763 mmol) and triethylamine (77 mg, 0.763 mmol) at 0°C. The resulting mixture was warmed to room temperature and stirred for 1 hr. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated to dryness to give the title compound as a solid. The solid was purified through silica gel column chromatography to give 280 mg(91%) of tan crystals, mp. 152-154°C.

1H NMR(CDCl₃) δ 8.07(brs,1H), 6.88(s,2H), 6.16(s,1H), 4.75(m,1H), 4.25(s,2H), 3.33(m,1H), 2.30(s,3H), 2.18(s,3H), 2.08(s,6H), 1.4-1.75(m,4H), 0.97(t,6H) ppm.

The following compounds were prepared by an analogous method to that in the preceding paragraph:

15 3-Chloro-N-[4-(1-ethyl-propylamino)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-3-yl]-propionamide

tan solid,mp. 183-185°C. Anal. For C₂₃H₃₂CIN₃O₂ calc, C, 66.09; H, 7.72; N, 10.05; found, C, 66.27; H, 7.87; N, 9.99.

20 2-Chloro-N-[4-(1-ethyl-propylamino)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-3-yl]-propionamide

mp. 170-172°C, Anal. For C₂₃H₃₂CIN₃O₂ calc. C, 66.09; H, 7.72; N, 10.05; found C, 66.20; H, 7.52; N, 10.09.

Example 3

25 N3-Allyl-N4-(1-ethyl-propyl)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridine-3,4-diamine

To a solution of N-4-(1-ethyl-propyl)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridine-3,4-diamine (500 mg, 1.52 mmol) in dry THF was added 1M in THF of lithium bis(trimethylsilyl)amide (1.6 ml, 1.6 mmol) at -78°C. After stirring at -78°C for 10 min, allyl bromide (0.13 ml, 1.52 mmol) was added and the resulting mixture was stirred at that temperature for 20 min, then warmed to room temperature overnight. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated to dryness to give the title compound as a green-blue oil. The oil was purified through silica gel column chromatography using 5%ethyl acetate in hexane as eluent to give a yellow crystal, mp. 86-88°C.

35 1H NMR(CDCl₃) δ 6.87(s,2H), 6.0(m,2H), 5.2-5.35(m,2H), 4.8(d,1H), 3.54(d,2H), 3.3(m,1H), 3.05(s,1H), 2.30(s,3H), 2.14(s,3H), 2.09(s,6H), 1.4-1.6(m,4H), 0.96(t,6H) ppm.

The following compounds were prepared by an analogous method:

N3-(3-Chloro-propyl)-N4-(1-ethyl-propyl)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridine-3,4-diamine

5 1H NMR(CDCl₃) d 6.85(s,2H), 6.05(s,1H), 4.9(d,1H), 3.8(m,2H), 3.3(m,1H),
3.1(m,2H), 2.3(s,3H), 2.159s,3H), 2.04(s,6H), 1.79m,2H), 1.5(m,2H), 1.0(m,6H) ppm.

N4-(1-Ethyl-propyl)-6-methyl-N3-propa-1,2-dienyl-2-(2,4,6-trimethyl-phenoxy)-pyridine-3,4-diamine

10 1H NMR(CDCl₃) d 8.93(d,1H), 6.86(s,2H), 6.66(m,1H), 6.09(s,1H), 5.4-5.6(m,2H),
5.54(d,1H), 3.27(m,1H), 2.27(s,3H), 2.12(s,3H), 2.05(s,6H), 1.6(m,4H), 0.94(t,6H) ppm.

Example 4

2-[3-Amino-2-(4-chloro-2,6-dimethyl-phenoxy)-6-methyl-pyridin-4-(S)-ylamino]-butan-1-ol

15 A mixture of 2-[2-(4-Chloro-2,6-dimethyl-phenoxy)-6-methyl-3-nitro-pyridin-4-(S)-ylamino]-butan-1-ol (120 mg) and Fe (73 mg) in 12 ml of 1:1 of AcOH:H₂O was heated at reflux for 2 hr. The reaction mixture was concentrated to dryness. The residue was quenched with water, basified to pH 12 and filtered through celite. The filtrate was extracted with chloroform. The organic layer was washed with brine, dried and concentrated to give the title compound as a yellow solid. The solid was purified through silica gel column chromatography using 1:1 EtOAc:hexane as eluent to give the title compound as a white solid, mp. 161-162°C.

20 1H NMR(CDCl₃) d 7.03(s,2H), 6.15(s,1H), 3.75(m,2H), 3.47(m,1H), 2.25(brs,3H),
2.08(s,6H), 1.5-1.8(m,2H), 0.98t,3H) ppm

Example 5

2-(4-Chloro-2,6-dimethyl-phenoxy)-4-(1-ethyl-propylamino)-6-methyl-nicotinic acid

25 methyl ester

A mixture of 4-chloro-6-methyl-2-(4-Chloro-2,6-dimethyl-phenoxy)-nicotinic acid methyl ester (77mg, 0.226 mmol) and 1-ethyl-propyl-amine in DMSO was heated at 120°C for 4 hr. The mixture was quenched with sat. ammonium chloride, water, brine and extracted with ethyl acetate. The organic layer was dried and concentrated to give 140 mg of yellow solid. 1HNMR(CDCl₃) d 8.10(d,1H), 7.03(s,2H), 6.09(s,1H), 3.88(s,3H), 3.35(m,1H), 2.10(s,3H), 2.08(s,6H), 1.5-1.7(m,4H), 0.96(t,6H) ppm.

Example 6

2-(4-Bromo-2,6-dimethyl-phenoxy)-4-(1-ethyl-propylamino)-6-methyl-nicotinic acid

methyl ester

35 A mixture of 4-chloro-6-methyl-2-(4-bromo-2,6-dimethyl-phenoxy)-nicotinic acid methyl ester and 1-ethyl-propyl-amine in DMSO was heated at 120°C for 16 hr. The mixture

was quenched with water, brine and extracted with ethyl acetate. The organic layer was dried and concentrated to dryness. The residue was purified through silica gel column chromatography using hexane to 3% ethyl acetate in hexane as eluent to give the title compound as a white solid. 1H NMR(CDCl₃) δ 8.1(d,1H), 7.18(s,2H), 6.08(s,1H), 3.87(s,3H),

- 5 3.35(m,1H), 2.10(s,3H), 2.08(s,6H), 1.4-1.7(m,4H), 0.96(t,6H) ppm.

Example 7

4-(1-Ethyl-prop-2-ynylamino)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-nicotinic acid methyl ester

A mixture of 4-chloro-6-methyl-2-(2,4,6-trimethyl-phenoxy)-nicotinic acid methyl ester
10 and 1-ethyl-propyl-amine in DMSO was heated at 130°C overnight. The mixture was quenched with water, brine and extracted with ethyl acetate. The organic layer was dried and concentrated to dryness. The residue was purified through silica gel column chromatography to give the title compound. 1H NMR(CDCl₃) δ 8.26(d,1H), 6.87(s,2H), 6.26(s,1H), 4.11(m,1H), 3.87(s,3H), 2.324(m,1H), 2.30(s,3H), 2.17(s,3H), 2.08(s,6H), 1.92(q,2H), 1.16(t,3H) ppm.

- 15 Example 8

4-(s)-(1-Hydroxymethyl-propylamino)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-nicotinic acid methyl ester

A mixture of 4-chloro-2-(2,4,6-trimethyl-phenoxy)-6-methyl-nicotinic acid methyl ester
20 (500 mg, 1.56 mmol) and (S)-2-amino-1-butanol (696 mg, 7.82 mmol) in DMSO was heated in 130°C oil bath for 24hr. The mixture cooled to rt and quenched with water and extracted with ethyl acetate. The organic layer was separated, washed with water, dried over anhydrous sodium sulfate, filtered, and concentrated to dryness to give 610 mg of crude product as an oil. The oil was purified through silica gel column chromatography using 30% ethyl acetate in hexane as eluent to give the title compound. Anal. calc. for C₂₁H₂₈N₂O₄. 1/2H₂O: C, 66.11; H, 7.66; N, 7.34; found: C, 66.27; H, 7.60; N, 7.21.

Example 9

4-(1-Ethyl-2-hydroxy-propylamino)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-nicotinic acid methyl ester

A mixture of 4-chloro-2-(2,4,6-trimethyl-phenoxy)-6-methyl-nicotinic acid methyl ester
30 (250 mg, 0.78 mmol) and 3-amino-pentan-2-ol (320 mg, 3.13 mmol) in DMSO was heated in 130°C oil bath for 24hr. The mixture cooled to rt and quenched with water and extracted with ethyl acetate. The organic layer was separated, washed with water, dried over anhydrous sodium sulfate, filtered, and concentrated to dryness to give 280mg of crude product as an oil. The oil was purified through silica gel column chromatography using 20% ethyl acetate in
35 hexane as eluent to give the title compound as a yellow solid, mp 116-120°C.

1H NMR(CDCl₃) d 8.17(m,1H), 6.87(s,2H), 6.21&6.14(two s, 1H), 3.88(s,3H), 3.8-4.0(m,2H), 3.5(m,1H), 3.3(m,1H), 2.30(s,3H), 2.12(s,3H), 2.09(s,6H), 1.8(d,1H), 1.5-1.8(m,2H), 1.26(d,3H), 0.99(t,3H) ppm.

Example 10

5 2-(4-Bromo-2,6-dimethyl-phenoxy)-4-(S)-(1-hydroxymethyl-propylamino)-6-methyl-nicotinic acid methyl ester

A mixture of 4-chloro-2-(4-bromo-2,6-trimethyl-phenoxy)-6-methyl-nicotinic acid methyl ester (850 mg) and (S)-2-amino-1-butanol in DMSO was heated in 130°C oil bath for 24hr. The mixture cooled to rt and quenched with water and extracted with ethyl acetate. The 10 organic layer was separated, washed with water, dried over anhydrous sodium sulfate, filtered, and concentrated to dryness to give 764mg of crude product as an oil. The oil was purified through silica gel column chromatography to give the title compound. 1H NMR (CDCl₃) d 8.15(d,1H), 7.16(s,2H), 6.18(s,1H), 3.86(s,3H), 3.72(m,1H), 3.70(m,1H), 3.54(m,1H), 2.10(s,3H), 2.06(s,6H), 1.5-1.8(m,2H), 1.00(t,3H) ppm.

15 Example 11

2-(4-Bromo-2,6-dimethyl-phenoxy)-4-(S)-(1-methoxymethyl-propylamino)-6-methyl-nicotinic acid methyl ester

A mixture of 4-chloro-2-(4-bromo-2,6-trimethyl-phenoxy)-6-methyl-nicotinic acid methyl ester and 1-methoxymethyl-propylamine in DMSO was heated in 130°C oil bath for 20 24hr. The mixture cooled to rt and quenched with water and extracted with ethyl acetate. The organic layer was separated, washed with water, dried over anhydrous sodium sulfate, filtered, and concentrated to dryness to give crude product. The crude compound was purified through silica gel column chromatography to give the title compound.

Example 12

25 2-(4-Chloro-2,6-dimethyl-phenoxy)-4-(1-hydroxymethyl-propylamino)-6-methyl-nicotinic acid methyl ester

A mixture of 4-chloro-2-(4-chloro-2,6-dimethyl-phenoxy)-6-methyl-nicotinic acid methyl ester (9.000g, 26.45 mmol) and (S)-2-amino-1-butanol (12.7ml) in 1-methyl-2-pyrrolidinone was heated at 130°C for 2 hr, then at 100°C overnight. The mixture cooled to rt 30 and poured into ice-water and diluted with ethyl acetate. The organic layer was separated, washed with water, dried over anhydrous sodium sulfate, filtered, and concentrated to dryness to give 13.6g of crude product as a light yellow oil. The oil was purified through silica gel column chromatography using chloroform to 2%MeOH in chloroform as eluent to give 6.6839 g (64%) of the title compound as a white glass foam. The glass foam was triturated 35 with hexane to give a white solid. The solid was recrystallized from di-iso-propyl ether to give

a white crystals, mp 122.5-124°C. Anal. calc. for C₂₀H₂₅ClN₂O₄: C, 61.14; H, 6.41; N, 7.13; found: C, 60.98; H, 6.43; N, 6.95.

Example 13

2-(4-Chloro-2-methoxy-phenoxy)-4-(S)-(1-hydroxymethyl-propylamino)-6-methyl-

5 nicotinic acid methyl ester

A mixture of 4-chloro-2-(4-Chloro-2-methoxy-phenoxy)-6-methyl-nicotinic acid methyl ester and (S)-2-amino-1-butanol in 1-methyl-2-pyrrolidinone was heated at 130°C overnight. The mixture cooled to room temperature and poured into ice-water and diluted with ethyl acetate. The organic layer was separated, washed with water, dried over anhydrous sodium sulfate, filtered, and concentrated to dryness. The residue was purified through silica gel column chromatography to give the title compound as a solid mp. 92.8-93.8°C, Anal. For C₁₉H₂₃N₂O₅Cl calc. C, 57.80; H, 5.87; 7.09; found, C, 57.70; H, 5.89; , 7.02.

Example 14

2-(4-Chloro-2,6-dimethyl-phenoxy)-4-(1-ethyl-2-hydroxy-propylamino)-6-methyl-

15 nicotinic acid methyl ester

A mixture of 4-chloro-2-(4-chloro-2,6-dimethyl-phenoxy)-6-methyl-nicotinic acid methyl ester (500 mg, 1.47 mmol) and 3-amino-pentan-2-ol (758mg, 7.35 mmol) in 1-methyl-2-pyrrolidinone was heated in 130°C oil bath for 24hr. The mixture cooled to rt and quenched with water and extracted with ethyl acetate. The organic layer was separated, washed with water, dried over anhydrous sodium sulfate, filtered, and concentrated to dryness to give an oil. The oil was purified through silica gel column chromatography using 20% ethyl acetate in hexane as eluent to give the title compound as a white crystal, mp 133-135°C.

1H NMR(CDCl₃) d 8.19(m,1H), 7.00(s,2H), 6.20&6.14(two sets of s,1H), 3.8-3.9(m,1H), 3.86(s,3H), 3.3&3.5(two sets of m,1H), 2.07(s,3H), 2.06(s,6H), 1.75(m,1H), 1.55(m,1H), 1.24(d,3H), 0.96(t,3H)ppm.

Example 15

2-(4-Chloro-2,6-dimethyl-phenoxy)-4-(1-ethyl-2-methoxy-propylamino)-6-methyl-
nicotinic acid methyl ester

To a solution of 2-(4-chloro-2,6-dimethyl-phenoxy)-4-(1-ethyl-2-hydroxy-propylamino)-

30 6-methyl-nicotinic acid methyl ester (50 mg, 0.123 mmol) in dry THF was added NaH and stirred for 20 min. An excess of MeI was added and the resulting mixture was stirred at rt overnight. The mixture cooled to rt and quenched with water and extracted with ethyl acetate. The organic layer was separated, washed with water, dried over anhydrous sodium sulfate, filtered, and concentrated to dryness to give an oil. The oil was purified through silica gel column chromatography using 20% ethyl acetate in hexane as an eluent to give the title

compound as a clear oil. ^1H NMR(CDCl_3) δ 8.20(d,1H), 7.00(s,2H), 6.14&6.10(two sets of s,1H), 3.859s,3H), 3.47(m,1H), 3.39&3.37(two sets of s,3H), 2.08(s,3H), 2.06(s,6H), 1.75(m,1H), 1.58(m,1H), 1.14(t,3H), 0.95(t,3H)ppm.

Example 16

- 5 2-(4-Chloro-2,6-dimethyl-phenoxy)-4-(1-ethyl-2-oxo-propylamino)-6-methyl-nicotinic acid methyl ester

The title compound was prepared by Dess-Martin oxidation of 2-(4-chloro-2,6-dimethyl-phenoxy)-4-(1-ethyl-2-hydroxy-propylamino)-6-methyl-nicotinic acid methyl ester. A white solid was obtained after silica gel column chromatography. ^1H NMR(CDCl_3) δ 8.6(d,1H), 7.01(s,2H), 5.899s,1H), 3.9-4.0(m,1H), 3.90(s,3H), 2.17(s,3H), 2.07(s,3H), 2.05(s,3H), 1.859m,1H), 1.93(m,1H), 1.00(t,3H) ppm.

Example 17

- 15 2-(4-Chloro-2,6-dimethyl-phenoxy)-4-(1-formyl-propylamino)-6-methyl-nicotinic acid methyl ester

15 The title compound was prepared by Dess-Martin oxidation of 2-(4-chloro-2,6-dimethyl-phenoxy)-4-(1-hydroxymethyl-propylamino)-6-methyl-nicotinic acid methyl ester. The title compound was obtained after column chromatography. ^1H NMR (CDCl_3) 9.54(d,1H), 8.56(d,1H), 7.01(s,2H), 5.93(s,1H), 3.92(m,1H), 3.89(s,3H), 2.08(s,3H), 2.05(s,6H), 1.05(t,3H) ppm.

- 20 Example 18

- 20 2-(4-Chloro-2,6-dimethyl-phenoxy)-4-(S)-(4-ethyl-2-oxo-oxazolidin-3-yl)-6-methyl-nicotinic acid methyl ester

A mixture of 2-(4-chloro-2,6-dimethyl-phenoxy)-4-(1-hydroxymethyl-propylamino)-6-methyl-nicotinic acid methyl ester (106 mg, 0.27 mmol), triphosgene (27 mg, 0.090 mmol), 25 triethylamine (27 mg, 0.27 mmol) in dry THF was stirred at room temperature for 2 hr. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was separated, washed with water, dried over anhydrous sodium sulfate, filtered, and concentrated to dryness to give 13.6g of crude product as a white glass foam. The foam was triturated with hexane/diethyl ether to give a white solid, mp. 144-145.5°C, Anal. For 30 $\text{C}_{21}\text{H}_{23}\text{ClN}_2\text{O}_5$ calc.: C, 60.22; H, 5.53; N, 6.69; found: C, 60.10, H, 5.79; N, 6.66.

Example 19

- 20 2-(4-Chloro-2,6-dimethyl-phenoxy)-4-(S)-{1-[(2-hydroxy-ethylamino)-methyl]-propylamino}-6-methyl-nicotinic acid methyl ester

To a solution of 2-(4-chloro-2,6-dimethyl-phenoxy)-4-(1-formyl-propylamino)-6-methyl-nicotinic acid methyl ester in dichloroethane was added 2-amino-ethanol, sodium 35 cyanoborohydride, acetic acid, anhydrous sodium sulfate. The resulting mixture was heated

at reflux and cooled to rt. The mixture was quenched with water and extracted with chloroform. The organic layer was separated, washed with water, dried over anhydrous sodium sulfate, filtered, and concentrated to dryness. After chromatography, the title compound was obtained as a white glass foam. 1H NMR(CDCl₃) δ 8.3(d,1H), 7.0(s,2H), 5 6.1(s,1H), 3.9(s,3H), 3.64(m,2H), 3.57(m,1H), 2.90(m,2H), 2.83(m,2H), 2.5(brs,2H), 2.09(s,3H), 2.06(s,6H), 1.65(m,2H), 0.97(t,3H) ppm.

Example 20

4-[Ethyl-(2-hydroxy-ethyl)-amino]-6-methyl-2-(2,4,6-trimethyl-phenoxy)-nicotinic acid methyl ester

10 A mixture of 4-chloro-6-methyl-2-(2,4,6-trimethyl-phenoxy)-nicotinic acid methyl ester and 1-ethyl-propyl-amine in 1-methyl-2-pyrrolidinone was heated at 130°C until starting material was consumed. The mixture was quenched with water, brine and extracted with ethyl acetate. The organic layer was dried and concentrated to dryness. The residue was purified through silica gel column chromatography to give the title compound. 1H
15 NMR(CDCl₃) δ 6.85(s,2H), 6.40(s,1H), 3.88(s,3H), 3.73(t,2H), 3.43(t,2H), 3.31(q,2H), 2.27(s,3H), 2.22(s,3H), 2.06(s,6H), 1.15(t,3H) ppm.

Example 21

4-[Ethyl-(2-methanesulfonyloxy-ethyl)-amino]-6-methyl-2-(2,4,6-trimethyl-phenoxy)-nicotinic acid methyl ester

20 A mixture of 4-[ethyl-(2-hydroxy-ethyl)-amino]-6-methyl-2-(2,4,6-trimethyl-phenoxy)-nicotinic acid methyl ester, methanesulfonyl chloride and triethylamine in methylene chloride was stirred at rt until all starting material were consumed. The mixture was quenched with water, brine and extracted with methylene chloride. The organic layer was dried and concentrated to dryness. The residue was purified through silica gel column chromatography
25 to give the title compound. 1H NMR(CDCl₃) δ 6.83(s,2H), 6.25(s,1H), 4.34(t,2H), 3.86(s,3H), 3.6(t,2H), 3.38(t,2H), 3.09(s,3H), 2.25(s,3H), 2.20(s,3H), 2.04(s,6H), 1.18(t,3H) ppm.

Example 22

4-[(2-Hydroxy-ethyl)-thiophen-2-ylmethyl-amino]-6-methyl-2-(2,4,6-trimethyl-phenoxy)-nicotinic acid methyl ester

30 A mixture of 4-chloro-6-methyl-2-(2,4,6-trimethyl-phenoxy)-nicotinic acid methyl ester and 2-[(thiophen-2-ylmethyl)-amino]-ethanol in 1-methyl-2-pyrrolidinone was heated at 130°C overnight. The mixture was quenched with water, brine and extracted with ethyl acetate. The organic layer was dried and concentrated to dryness. The residue was purified through silica gel column chromatography to give the title compound. 1H NMR (CDCl₃) δ 7.22(m,1H),
35 6.94(m,2H), 6.84(s,2H), 6.44(s,1H), 4.52(s,2H), 3.91(s,3H), 3.679(t,2H), 3.369(t,2H), 2.279(s,3H), 2.20(s,3H), 2.07(s,6H) ppm.

Example 23

The following compounds were prepared by the method analogous to that in Example 5, starting with an appropriate 4-chloro-6-methyl-2-(substituted-phenoxy)-nicotinic acid alkyl ester with an appropriate alkyl- or dialkyl-amino.

- 5 4-(2,2-Dimethyl-4-phenyl-[1,3]dioxan-5-ylamino)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-nicotinic acid methyl ester
 1H NMR (CDCl₃) d 8.71(d,2H), 7.1-7.4(m,5H), 6.82(s,2H), 5.55(s,1H), 5.229s,1H), 4.29(d,1H), 3.97(d,1H), 3.869s,3H), 3.61(d,1H), 2.25(s,3H), 2.01(s,6H), 1.91(s,3H), 1.65(s,3H), 1.61(s,3H) ppm.
- 10 2-(4-Chloro-2,6-dimethyl-phenoxy)-4-(S)-(1-hydroxymethyl-propylamino)-6-methyl-nicotinic acid ethyl ester
 1H NMR(CDCl₃) d 8.01(d,1H), 7.02(s,2H), 6.17(s,1H), 4.33(q,2H), 3.71(m,1H), 3.66(m,1H), 3.54m,1H), 2.10(s,3H), 2.07(s,6H), 1.5-1.8(m,2H), 1.33(t,3H), 1.00(t,3H) ppm.
 4-[Ethyl-(2-methoxy-ethyl)-amino]-6-methyl-2-(2,4,6-trimethyl-phenoxy)-nicotinic acid methyl ester
 1H NMR(CDCl₃) d 6.83(s,2H), 6.19(s,1H), 3.869s,3H), 3.35-3.6(m,4H), 3.35(s,3H), 2.26(s,3H), 2.15(s,3H), 2.06(s,6H), 1.179t,3H) ppm.
 2-(4-Chloro-2,6-dimethyl-phenoxy)-4-(S,R)-&(S,S)-(1-ethyl-2-hydroxy-propylamino)-6-methyl-nicotinic acid methyl ester
 1H NMR(CDCl₃) d 8.2(d,1H), 7.01(s2H), 6.20(s, 0.2H), 6.15(s,0.8H), 3.92(m,1H), 3.87(s,3H), 3.48(m,0.2H), 3.31(m,0.8H), 2.08(s,3H), 2.06(s,6H), 1.5-1.8(m,2H), 1.25(d,3H), 0.96(t,3H) ppm.
 2-(4-Chloro-2,6-dimethyl-phenoxy)-4-(R)-(1-hydroxymethyl-propylamino)-6-methyl-nicotinic acid methyl ester
 1H NMR(CDCl₃) 8.12(d,1H), 7.00(s,2H), 6.16(s,1H), 3.85(s,3H), 3.6-3.8(m,2H), 3.53(m,1H), 2.08(s,3H), 2.05(s,6H), 1.5-1.8(m,2H), 0.98(t,3H)ppm.
 4-(2-Hydroxy-1-hydroxymethyl-ethylamino)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-nicotinic acid methyl ester
 1H NMR(CDCl₃) d 8.44(d,1H), 6.84(s,2H), 6.17(s,1H), 3.8-4.0(m,4H), 3.85(s,3H), 3.70(m,1H), 2.60(s,3H), 2.27(s,3H), 2.11(s,2H), 2.05(s,6H) ppm.
 4-(2-Methoxy-1-methoxymethyl-ethylamino)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-nicotinic acid methyl ester
 1H NMR(CDCl₃) d 8.38(d,1H), 6.88(s,2H), 6.18(s,1H), 3.88(s,3H), 3.78(m,1H), 3.56(m,2H), 3.44(s,6H), 2.31(s,3H), 2.15(s,3H), 2.09(s,6H) ppm.

4-(1-Hydroxymethyl-2-methoxy-ethylamino)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-nicotinic acid methyl ester

1H NMR(CDCl₃) d 8.44(d,1H), 6.88(s,2H), 6.21(s,1H), 3.89(s,3H), 3.80(m,1H), 3.5-3.7(m,2H), 3.45(s,3H), 2.31(s,3H), 2.16(s,3H), 2.09(s,6H) ppm.

5 2-(4-Chloro-2,6-dimethyl-phenoxy)-4-(1-ethyl-2-hydroxy-butylamino)-6-methyl-nicotinic acid methyl ester

1H NMR (CDCl₃) d 8.34(d,1H), 7.069s,2H), 6.16(s,1H), 3.91(s,3H), 3.70(m,1H), 3.5(m,1H), 2.13(s,3H), 2.11(s,6H), 1.5-1.9(m,4H), 1.01(m,6H) ppm.

Example 24

10 [2-(4-Chloro-2,6-dimethyl-phenoxy)-4-(1-ethyl-propylamino)-6-methyl-pyridin-3-yl]-methanol

A mixture of 4-(1-ethyl-propylamino)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-nicotinic acid methyl ester (130 mg, 0.332 mmol) and an excess of 1M diisobutyl aluminum hydride in THF in dry THF was stirred at -78°C for 10 min, then warmed to rt. The mixture was quenched with methanol and stirred at room temperature for 20 min, filtered through celite and washed with methanol and chloroform. The filtrate was concentrated to dryness. The residue was purified through silica gel column chromatography to give the title compound. 1HNMR(CDCl₃) d 7.03(s,2H), 6.11(s,1H), 5.03(d,1H), 4.96(s,2H), 3.32(m,1H), 2.14(s,3H), 2.07(s,6H), 1.4-1.7(m,4H), 0.96(t,6H) ppm.

20 [2-(4-Bromo-2,6-dimethyl-phenoxy)-4-(1-ethyl-propylamino)-6-methyl-pyridin-3-yl]-methanol

The title compound was prepared by the method analogous to that in the preceding paragraph. 1H NMR(CDCl₃) d 7.18(s,2H), 6.11(s,1H), 5.05(d,1H), 4.91(d,2H), 3.31(m,1H), 2.14(s,3H), 2.07(s,6H), 1.4-1.7(m,4H), 0.96(t,6H) ppm.

25 Example 25

2-[3-Hydroxymethyl-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-(S)-ylamino]-butan-1-ol

A mixture of 4-(S)-(1-hydroxymethyl-propylamino)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-

30 nicotinic acid methyl ester and 1M lithium aluminum hydride and aluminum chloride in THF in dry THF was heated at reflux. The mixture was cooled and quenched with water, 2N NaOH, then of water and stirred at room temperature for 10 min. White solid formed and was filtered through celite, washed with THF. The filtrate was concentrate to dryness to give the title compound as a white solid after column chromatography,

35 mp. 135-137°C; Anal. For C₂₀H₂₈N₂O₃ calc. C, 69.74; H, 8.19; N, 8.13; found C, 69.42; H, 8.34; N, 7.95

The following compounds were prepared by a method analogous to that in the preceding paragraph, starting with the corresponding ester and reaction thereof with lithium aluminum hydride and aluminum chloride.

- 3-[2-(4-Chloro-2,6-dimethyl-phenoxy)-3-hydroxymethyl-6-methyl-pyridin-4-ylamino]-pentan-2-ol
- 5 mp. 180-182°C. 1H NMR(CDCl₃) 7.0(s,2H), 6.18&6.15(two sets of s,1H), 5.1 and 5.22(m,1H), 4.92(m,2H), 3.80-4.0(m,1H), 3.20-3.5(m,1H), 2.11(s,3H), 2.04(s,6H), 1.4-1.8(m,2H), 1.23(m,3H), 0.98(m,3H) ppm.
- 2-[2-(2,6-Dimethyl-phenoxy)-3-hydroxymethyl-6-methyl-pyridin-4-ylamino]-butan-1-ol
- 10 1H (CDCl₃) d 7.05(m,3H), 6.20(s,1H), 4.8-5.0(m,2H), 3.74(m,1H), 3.66(m,1H), 3.50(m,1H), 2.0-2.29(m,9H), 1.55-1.75(m,2H), 0.99(t,3H) ppm.
- 3-[3-Hydroxymethyl-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-ylamino]-pentan-2-ol
- 15 1H NMR(CDCl₃) d 6.86(s,2H), 6.17(s, 1H), 4.0(d,1H), 3.9(m,1H), 3.3(m,1H), 2.29(s,3H), 2.14(s,3H), 2.13(s,3H), 2.07(s,6H), 1.8(d,1H), 1.4-1.8(m,2H), 1.25(d,3H), 0.99(t,3H) ppm.
- 2-[2-(4-Chloro-2-methoxy-phenoxy)-3-hydroxymethyl-6-methyl-pyridin-4-ylamino]-butan-1-ol
- 20 1H NMR(CDCl₃) 6.8-7.0(m,3H), 6.2(s,1H), 5.02(d,1H), 4.7(ABq,2H), 3.74(m,5H), 3.350-3.5(m,2H), 2.9(brs,2H), 2.18(s,3H), 1.4-1.7(m,2H), 1.23(m,3H), 0.95(t,3H) ppm.

Example 26

- 2-[2-(4-Chloro-2,6-dimethyl-phenoxy)-3-hydroxymethyl-6-methyl-pyridin-4-ylamino]-butan-1-ol
- A mixture of 4-(s)-(1-hydroxymethyl-propylamino)-6-methyl-2-(4-chloro-2,6-dimethyl-phenoxy)-nicotinic acid methyl ester and 1M lithium aluminum hydride in THF was stirred at rt for 2 hr. The mixture was cooled and quenched with water, 2N NaOH, then of water and stirred at room temperature for 10 min. White solid formed and was filtered through celite, washed with THF. The filtrate was concentrated to dryness to give the title compound as a white solid after column chromatography, mp 133-135°C. 1H NMR(CDCl₃) 7.00(s,2H), 6.17(s,1H), 5.12(d,1H), 4.90(m,2H), 3.4-3.8(m,3H), 2.12(s,3H), 2.04(s,6H), 1.4-1.6(m,2H), 0.99(t,3H) ppm.

The following compounds were prepared by the method analogous to that in the preceding paragraph, starting with the corresponding methyl ester with lithium aluminum hydride:

2-[Ethyl-[3-hydroxymethyl-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-amino]-ethanol

1H NMR(CDCl₃) d 1H NMR(CDCl₃) 6.86(s,2H), 6.53(s,1H), 4.94(s,2H), 3.67(m,2H), 3.1-3.3 (m,4H), 2.28(s,3H), 2.20(s,3H), 2.04(s,6H), 1.09(t,3H) ppm.

5 4-[2-(4-Chloro-2,6-dimethyl-phenoxy)-3-hydroxymethyl-6-methyl-pyridin-4-ylamino]-hexan-3-ol

mp. 145-148°C. 1H NMR(CDCl₃) d 1H NMR(CDCl₃) 7.05(s,2H), 6.16(s,1H), 5.3(d,1H), 4.94(s,2H), 3.67(m,1H), 3.40 (m,1H), 2.151(s,3H), 2.09(s,6H), 1.4-1.8(m,4H), 1.23(m,3H), 1.02(m,6H) ppm.

10 2-[2-(4-Chloro-2-methoxy-phenoxy)-3-hydroxymethyl-6-methyl-pyridin-4-(S)-ylamino]-butan-1-ol

1H NMR (CDCl₃) d 7.8-7.95(m,2H), 5.02(d,1H), 4.74(ABq,2H), 3.74(s,3H), 3.72(m,2H), 3.45m,1H), 2.98(brs,1H), 2.18(s,3H), 1.4-1.7(m,2H), 0.95(t,3H) ppm.

15 4-[2-(4-Chloro-2,6-dimethyl-phenoxy)-3-hydroxymethyl-6-methyl-pyridin-4-ylamino]-hexan-3-ol

1H NMR (CDCl₃) d 7.05(s,2H), 6.16(s,1H), 5.30(d,1H), 4.94(s,2H), 3.67(m,1H), 3.4(m,1H), 2.15(s,3H), 2.09(s,6H), 1.5-1.9(m,4H), 1.01(m,6H) ppm.

[2-(2,4-Dimethoxy-phenylamino)-4-(1-methoxymethyl-propoxy)-6-methyl-pyridin-3-yl]-methanol

20 1H NMR(CDCl₃) d 6.90(d,1H), 6.42(s,1H), 6.40(d,1H), 5.91(s,1H), 4.42(m,1H), 4.28(s,2H), 3.79(s,3H), 3.76(s,3H), 3.56(m,2H), 3.40(s,3H), 2.33(s,3H), 1.5-1.85(m,2H), 1.02(t,3H) ppm.

Example 27

2-(4-Chloro-2,6-dimethyl-phenoxy)-4-(S)-(1-hydroxymethyl-propylamino)-6-methyl-nicotinic acid

A mixture of 2-(4-chloro-2,6-dimethyl-phenoxy)-4-(S)-(1-hydroxymethyl-propylamino)-6-methyl-nicotinic acid methyl ester (113 mg) and lithium hydroxide in dioxane/THF/water was stirred at room temperature over night. The mixture was quenched with ammonium chloride and extracted with chloroform. The organic layer was dried and concentrated to give 78mg of the title compound as a white solid. 1H NMR(CDCl₃) d 10.55(brs,1H), 9.2(d,1H), 7.06(s,2H), 6.3(s,1H), 3.5-3.8(m,3H), 2.11(s,3H), 2.09(s,3H), 2.08(s,3H), 1.78(m,1H), 1.62(m,1H), 1.00(t,3H) ppm.

4-(1-Ethyl-prop-2-ynylamino)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-nicotinic acid

mp. 131-133°C, 1H NMR(CDCl₃) d 11.29(brs,1H), 9.35(d,1H), 6.91(s,2H), 6.38(s,1H), 4.12(m,1H), 2.88(m,1H), 2.32(s,3H), 2.19(s,3H), 2.09(s,6H), 1.96(m,2H), 1.17(t,6H) ppm.

2-(4-Bromo-2,6-dimethyl-phenoxy)-4-(S)-(1-methoxymethyl-propylamino)-6-methyl-nicotinic acid

1H NMR (CDCl₃) d 10.5(brs, 1H), 8.6(d,1H), 7.15(d,2H), 6.25(s,1H), 3.3-3.6(m,3H), 3.38(s,3H), 2.11(s,3H), 2.09(s,3H), 2.08(s,3H), 1.5-1.85(m,2H), 0.91(t,3H) ppm.

5 4-(2-Methoxy-1-methoxymethyl-ethylamino)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-nicotinic acid

1H NMR(CDCl₃) d 9.44(d,1H), 6.92(s,2H), 6.30(s,1H), 3.80(m,1H), 3.58(m,2H), 3.44(s,6H), 2.33(s,3H), 2.16(s,3H), 2.10(s,6H) ppm.

Example 28

10 The following compounds were prepared by reacting the corresponding [2-(substituted-phenoxy)-3-chloromethyl-6-methyl-pyridin-4-yl]-alkyl-amine with an appropriate amine.

[2-(4-Chloro-2,6-dimethyl-phenoxy)-3-isobutoxymethyl-6-methyl-pyridin-4-yl]-[1-ethyl-propyl]-amine

15 1H NMR(CDCl₃) d 6.94(s,2H), 6.0(s,1H), 5.13(d,1H), 4.7(s,2H), 3.2(m,1H), 3.16(d,2H), 2.02(s,3H), 1.96(s,6H), 1.8(m,1H), 1.3-1.6(m,4H), 0.82(t,6H), 0.8(d,6H) ppm.

[3-Ethoxymethyl-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-[1-ethyl-propyl]-amine

20 1H NMR (CDCl₃) d 6.86(s,2H), 6.03(s,1H), 5.30(d,1H), 4.83(s,2H), 3.58(q,2H), 3.35(m,1H), 2.29(s,3H), 2.15(s,3H), 2.06(s,6H), 1.5-1.78(m,4H), 1.23(t,3H), 0.967(t,6H)ppm.

2-[3-Butoxymethyl-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-ylamino]-butan-1-ol

1H NMR(CDCl₃) d 6.85(s,2H), 6.179s,1H), 5.3(d,1H), 4.82(Abq,2H), 3.5-3.8(m,2H), 3.5(t,2H), 2.3(s,3H), 2.15(s,3H), 2.02(s,6H), 1.75(brs,1H), 1.5-1.8(m,4H), 1.3-1.5(m,2H), 1.02(t,3H), 0.9(t,3H) ppm.

25 Example 29

1-[4-(1-Ethyl-propylamino)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-3-yl]-ethanol

The title compound was prepared by reacting 4-(1-ethyl-propylamino)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridine-3-carbaldehyde with methylolithium lithium in THF at -78°C. The desired product was isolated after silica gel column chromatography to give 60.1% of a colorless oil. 1H NMR(CDCl₃) d 6.87(s,2H), 6.06(s,1H), 5.7(q,1H), 3.3(m,1H), 2.29(s,3H), 2.12(s,6H), 2.069s,3H), 1.4-1.7(m,4H), 1.59(d,3H), 0.8-1.0(m,6H) ppm.

Example 30

Acetic acid 4-(1-ethyl-propylamino)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-3-ylmethyl ester

35 The title compound was obtained by acetylation of [2-(2,4,6-trimethyl-phenoxy)-3-hydroxymethyl-6-methyl-pyridin-4-yl]-[1-ethyl-propyl]-amine.

1H NMR(CCl₃) d 6.84(s,2H), 6.04(s,1H), 5.35(s,2H), 5.23(d,1H), 3.32(m,1H), 2.28(s,3H), 2.12(s,3H), 2.08(s,3H), 2.07(s,6H), 1.4-1.7(m,4H), 0.93(t,6H) ppm.

Example 31

2-[2-(4-Chloro-2,6-dimethyl-phenoxy)-3-(1-hydroxy-1-methyl-ethyl)-6-methyl-pyridin-4-(S)-ylamino]-butan-1-ol

The title compound was prepared by reacting 2-(4-chloro-2,6-dimethyl-phenoxy)-4-(1-hydroxymethyl-propylamino)-6-methyl-nicotinic acid methyl ester with an excess of 1M methyl magnesium bromide in THF at room temperature overnight. Standard work-up procedure gave the title compound after silica gel chromatography.

1H NMR(CDCl₃) d 7.4(brs,1H), 7.01(s,2H), 6.13(s,1H), 3.7(m,1H), 3.6(m,1H), 3.45(m,1H), 2.04(s,3H), 2.03(s,3H), 2.02(s,3H), 1.5-1.7(m,2H), 0.98(t,3H) ppm.

Example 32

[2-(4-Chloro-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridin-4-yl]-(1-ethyl-propyl)-amine

To a solution of [2-(4-Chloro-2,6-dimethyl-phenoxy)-3-chloromethyl-6-methyl-pyridin-4-yl]-(1-ethyl-propyl)-amine (75 mg, 0.196 mmol) in dry THF was added 1.0M BH₃ in THF (0.59 ml, 0.59 mmol) and stirred for 2 hr. The mixture was quenched with dilute HCl and stirred for 5 min. The reaction mixture was neutralized with 2N NaOH, water and extracted with ethyl acetate. The organic layer was separated, dried and concentrated to dryness. The residue was purified through silica gel column chromatography to give the title compound as a colorless oil.

1H NMR(CDCl₃) d 7.03(s,2H), 6.08(s,1H), 3.73(d,1H), 3.3(m,1H), 2.15(s,3H), 2.12(s,3H), 2.08(s,6H), 1.4-1.6(m,4H), 0.96(t,6H) ppm.

Example 33

[2-(2,6-Dimethyl-phenoxy)-3,6-dimethyl-pyridin-4-yl]-(1-ethyl-propyl)-amine

To a solution of [2-(4-bromo-2,6-dimethyl-phenoxy)-4-(1-ethyl-propylamino)-6-methyl-pyridin-3-yl]-methanol (43 mg, 0.106 mmol) in dry THF was added 1.0M lithium aluminium hydride in diethyl ether (0.25 ml) and aluminum chloride (28 mg). The resulting mixture was stirred at room temperature overnight. The mixture was quenched with water, 2NaOH, then water. Solid formed and filtered through celite, washed with THF, then chloroform. The filtrate was concentrated to dryness. The residue was diluted with water and ethyl acetate. The organic layer was separated, dried and concentrated to give the crude material. The title compound was isolated after silica gel chromatography. 1H NMR(CDCl₃) d 6.9-7.1(m,3H), 6.07(s,1H), 3.35(d,1H), 3.33(m,1H), 2.14(s,3H), 2.13(s,3H), 2.12(s,6H), 1.5-1.8(m,4H), 0.97(t,6H) ppm.

Example 34[2-(4-Bromo-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridin-4-yl]-(1-ethyl-propyl)-amine

The title compound was prepared by the method analogous to that in Example 145 as a white solid. 1H NMR(CDCl₃) d 7.19(s,2H), 6.09(s,1H), 3.36(d,1H), 3.33(m,1H), 2.15(s,3H), 5 2.12(s,3H), 2.09(s,6H), 1.4-1.8(m,4H), 0.97(t,6H) ppm.

Example 354-[4-(1-Ethyl-propylamino)-3,6-dimethyl-pyridin-2-yloxy]-3,5-dimethyl-benzaldehyde

To a solution of [2-(4-bromo-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridin-4-yl]-(1-ethyl-propyl)-amine in dry THF was added n-butyllithium at -78°C. After stirring at -78°C for 10 min, n,N-dimethylformamide was added and the resulting mixture was stirred at -78°C for 20 min, the dry-ice bath was removed. After stirring for 5 min, the mixture was quenched with diluted HCl, water and adjusted to pH7.5 and extracted with ethyl acetate. The organic layer was separated, dried, and concentrated to dryness. The residue was purified through silica gel chromatography to give the title compound. 1H NMR(CDCl₃) d 9.93(s,1H), 7.60(s,2H), 15 6.10(s,1H), 3.75(d,1H), 3.35(m1H), 2.17(s,6H), 2.13(s,3H), 2.12(s,3H), 1.4-1.8(m,4H), 0.97(t,6H) ppm.

Example 36{4-[4-(1-Ethyl-propylamino)-3,6-dimethyl-pyridin-2-yloxy]-3,5-dimethyl-phenyl}-methanol

20 A mixture of 4-[4-(1-Ethyl-propylamino)-3,6-dimethyl-pyridin-2-yloxy]-3,5-dimethyl-benzaldehyde and sodium borohydride in methanol was stirred at room temperature. After standard work-up procedure and purification, the title compound was obtained as a solid. 1H NMR(CDCl₃) d 7.06(s,2H), 6.08(s,1H), 4.64(s,2H), 3.74(d,1H), 3.33(m,1H), 2.14(s,3H), 2.13(s,3H), 2.11(s,6H) ppm.

Example 37(1-Ethyl-propyl)-[2-(4-methoxymethyl-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridin-4-yl]-amine

To a solution of {4-[4-(1-Ethyl-propylamino)-3,6-dimethyl-pyridin-2-yloxy]-3,5-dimethyl-phenyl}-methanol in dry THF was added 60% NaOH in oil and stirred for 5 min. 30 Excess of Mel was added and stirred at room temperature for 2hr. After standard worked up procedure and purification, the title compound was obtained as a clear golden oil. 1H NMR(CDCl₃) d 7.02(s,2H), 6.06(s,1H), 4.40(s,3H), 3.72(d,1H), 3.39(s,3H), 3.36(m,1H), 2.12(s,3H), 2.11(s,3H), 2.10(s,6H), 1.4-1.7(m,4H), 0.95(t,6H) ppm.

Example 38[2-(4-Ethyl-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridin-4-yl]-(1-ethyl-propyl)-amine

To a solution of [2-(4-bromo-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridin-4-yl]-(1-ethyl-propyl)-amine in dry THF was added n-butyllithium at -78°C. After stirring at -78°C for 10 min, ethyl iodide was added and the resulting mixture was stirred at -78°C for 30 min, the dry-ice bath was removed. After stirring for 5 min, the mixture was quenched with brine and extracted with ethyl acetate. The organic layer was separated, dried, and concentrated to dryness. The residue was purified through silica gel chromatography to give the title compound. 1H NMR(CDCl₃) d 6.89(s,2H), 6.07(s,1H), 3.72(d,1H), 3.34(m,1H), 2.58(q,2H), 2.16(s,3H), 2.12(s,3H), 2.09(s,6H), 1.4-1.7(m,4H), 1.25(t,3H), 0.96(t,6H) ppm.

Example 392-[4-[4-(1-Ethyl-propylamino)-3,6-dimethyl-pyridin-2-yloxy]-3,5-dimethyl-phenyl]-propan-2-ol

To a solution of [2-(4-bromo-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridin-4-yl]-(1-ethyl-propyl)-amine in dry THF was added n-butyllithium at -78°C. After stirring at -78°C for 10 min, acetone was added and the resulting mixture was stirred at -78°C for 30 min. The dry-ice bath was removed. After stirring for 5 min, the mixture was quenched with brine and extracted with ethyl acetate. The organic layer was separated, dried, and concentrated to dryness. The residue was purified through silica gel chromatography to give the title compound. 1H NMR(CDCl₃) d 7.17(s,2H), 6.08(s,1H), 3.73(d,1H), 3.33(m,1H), 2.19(s,3H), 2.15(s,3H), 2.12(s,6H), 1.4-1.7(m,4H), 1.26(s,6H), 0.96(t,6H) ppm.

Example 401-[4-[4-(1-Ethyl-propylamino)-3,6-dimethyl-pyridin-2-yloxy]-3,5-dimethyl-phenyl]-ethanol

To a solution of [2-(4-bromo-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridin-4-yl]-(1-ethyl-propyl)-amine in dry THF was added n-butyllithium at -78°C. After stirring at -78°C for 10 min, acetaldehyde was added and the resulting mixture was stirred at -78°C for 30 min, the dry-ice bath was removed. After stirring for 5 min, the mixture was quenched with brine and extracted with ethyl acetate. The organic layer was separated, dried, and concentrated to dryness. The residue was purified through silica gel chromatography to give the title compound. 1H NMR(CDCl₃) d 7.06(s,2H), 4.84(m,1H), 6.08(s,1H), 3.73(d,1H), 3.35(m,1H), 2.14(s,3H), 2.12(s,3H), 2.11(s,6H), 1.4-1.7(m,4H), 1.51(d,3H), 0.96(t,6H) ppm.

Example 41(1-Ethyl-propyl)-[2-(4-isopropenyl-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridin-4-yl]-amine

The title compound was prepared by reacting of 2-[4-[4-(1-Ethyl-propylamino)-3,6-dimethyl-pyridin-2-yloxy]-3,5-dimethyl-phenyl]-propan-2-ol with Burgess Inner salt ($\text{Et}_3\text{NS}(\text{O})_2\text{NCOOMe}$) in benzene at reflux for 30 min. ^1H NMR(CDCl_3) d 7.17(s,2H), 6.08(s,1H), 5.34(s,1H), 5.02(s,1H), 3.72(d,1H), 3.32(m,1H), 2.12 and 2.15 (two sets of s, 12H), 1.4-1.6(m,4H), 0.97(t,6H) ppm.

Example 42(1-Ethyl-propyl)-[2-(4-isopropyl-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridin-4-yl]-amine

The title compound was prepared by hydrogenation of (1-ethyl-propyl)-[2-(4-isopropenyl-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridin-4-yl]-amine using 10% Pd/C as catalyst in ethyl acetate at 55 psi until all starting material were consumed. The title compound was obtained as an oil after purification. ^1H NMR(CDCl_3) d 6.93(s,2H), 6.10(s,1H), 3.73(brs,1H), 3.36(m,1H), 2.18(s,3H), 2.14(s,3H), 2.12(s,6H), 1.4-1.8(m,4H), 1.27(d,6H), 0.98(t,6H) ppm.

Example 43[3,6-Dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-[1-ethyl- allyl]-amine

The title compound was prepared as a clear oil by reduction of 4-(1-Ethyl-prop-2-ynylamino)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-nicotinic acid with lithium aluminum hydride and aluminum chloride. ^1H NMR(CDCl_3) d 6.87(s,2H), 6.08(s,1H), 5.7-5.9(m,1H), 5.1-5.3(m,2H), 3.75-4.0(m,2H), 2.30(s,3H), 2.16(s,3H), 2.15(s,3H), 2.08(s,6H), 1.70(m,2H), 1.03(t,3H)ppm.

Example 44(1-Ethyl-propyl)-[2-(4-fluoro-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridin-4-yl]-amine

To a solution of [2-(4-bromo-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridin-4-yl]-[1-ethyl-propyl]-amine in dry THF was added n-butyllithium at -78°C . After stirring at -78°C for 10 min, $(\text{PhSO}_2)_2\text{NF}$ was added and the resulting mixture was stirred at -78°C for 30 min, the dry-ice bath was removed. After stirring for 5 min, the mixture was quenched with brine and extracted with ethyl acetate. The organic layer was separated, dried, and concentrated to dryness. The residue was purified through silica gel chromatography to give the title compound. ^1H NMR(CDCl_3) d 6.77(s,1H), 6.73(s,1H), 6.08(s,1H), 3.3(m,1H), 2.12(s,3H), 2.09(s,6H), 2.08(s,3H), 1.4-1.8(m,4H), 0.97(t,6H)ppm.

Example 452-[2-(2,6-Dimethyl-phenoxy)-3,6-dimethyl-pyridin-4-ylamino]-butan-1-ol

The title compound was prepared by the method analogous to that in Example 33.

1H NMR(CDCl₃) d 7.05(m,3H), 6.24(s,1H), 3.4-3.8(m,3H), 2.24(s,3H), 2.16(s,3H),
5 2.10(s,6H), 1.5-1.8(m,2H), 0.99(t,3H)ppm.

Example 462-[3,6-Dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-(S)-ylamino]-butan-1-ol

To a solution of 2-(2,4,6-trimethyl-phenoxy)-4-(1-hydroxymethyl-propylamino)-6-methyl-nicotinic acid methyl ester in dry THF was added 1.0M lithium aluminium hydride in diethyl ether (0.25 ml) and aluminum chloride. The resulting mixture was heated at reflux for 2 hr. The mixture was quenched with of water, 2NaOH, then water and stirred. Solid formed and was filtered through celite, then washed with water and ethyl acetate. The organic layer was separated, dried, concentrated, and purification to give the title compound as a white solid. Anal. For C₂₀H₂₈N₂O₂.1/2H₂O calc. C, 70.90; H, 8.52; N, 8.01; found C, 71.18; H, 8.66;

15 N, 8.30

The following compounds were prepared by the method analogous to that in the preceding paragraph, using the corresponding 2-(substituted phenoxy)-4-(alkyl-amino)-6-methyl-nicotinic acid methyl ester with lithium aluminum hydride and aluminum chloride.

3-[3,6-Dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-ylamino]-pentan-2-ol

20 1H NMR(CDCl₃) d 6.86(s,2H), 6.17&6.13(two sets of s, 1H), 5.0-5.2(m,1H), 4.9(s,2H),
3.9-4.1(m,1H), 3.5(m,1H), 3.3(m,1H), 2.29(s,3H), 2.14(s,3H), 2.08(s,6H), 1.4-1.8(m,2H),
1.27(m,3H), 0.98(m,3H) ppm.

3-[2-(4-Chloro-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridin-4-ylamino]-pentan-2-ol

25 1H NMR(CDCl₃) d 7.01(s,2H), 6.14&6.11(two sets of s,1H), 4.04&3.82(two sets of d,1H),
3.92(m,1H), 3.4&3.2(m,1H), 2.13(s,3H), 2.11(s,3H), 2.05(s,6H), 1.4-1.8(m,2H),
1.25(two sets of d, 3H), 0.98&0.96(two sets of t,3H) ppm.

Example 47Benzyl-[3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-ethyl-amine

A mixture of 4-bromo-3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridine (250 mg, 0.78 mmol), benzylethylamine (127 mg, 0.937 mmol), Pd(OAc)₂(3.6 mg, 0.0156 mmol), (S)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) (9.7 mg, 0.0156 mmol), potassium t-butoxide (105 mg, 0.781 mmol) in 25 ml of toluene was heated at reflux for 2 hr. The mixture was cooled to rt, quenched with water and extracted with ethyl acetate. The organic layer was separated, dried (Na₂SO₄), filtered, and concentrated to give a brown oil. The crude material 35 was purified through silica gel column chromatography to give the title compound. 1H

NMR(CDCl₃) d 7.2-7.4(m,5H), 6.86(s,2H), 6.41(s,1H), 4.23(s,2H), 3.07(q,2H), 2.31(s,3H), 2.29(s,3H), 2.16(s,3H), 2.06(s,6H), 1.05(t,3H) ppm.

The following compounds were prepared by the method analogous to that in the preceding paragraph, using an appropriate 4-bromo-2-(substituted phenoxy)-3-methyl-6-alkyl or alkoxy-pyridine with an appropriate amine.

[2-(4-Chloro-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridin-4-yl]-(1-methoxymethyl-propyl)-amine

1H NMR(CDCl₃) d 7.06(s,2H), 6.13(s,1H), 4.14(d,1H), 3.3-3.6(m,3H), 3.42(s,3H), 2.16(s,3H), 2.14(s,3H), 2.09(s,6H), 1.5-1.8(m,2H), 1.03(t,3H) ppm.

10 2-[3,6-Dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-ylamino]-3-phenyl-propan-1-ol

1H NMR(CDCl₃) d 8.6(d,1H), 7.2-7.4(m,5H), 6.84(s,2H), 6.169s,1H), 4.099d,1H), 3.82(m,1H), 3.5-3.7(m,2H), 2.95(d,2H), 2.96(s,3H), 2.27(s,3H), 2.14(s,3H), 2.05(s,6H) ppm.

[2-(4-Chloro-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridin-4-yl]-(1-methoxymethyl-propyl)-amine

15 1H NMR(CDCl₃) d 7.06(s,2H), 6.13(s,1H), 4.2(m,1H), 3.53(m,2H), 3.42(s,3H), 2.19(s,3H), 2.14(s,3H), 2.10(s,6H), 1.5-1.8(m,2H), 1.03(t,3H) ppm.

[2-(4-Chloro-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridin-4-yl]-(1-ethoxymethyl-propyl)-amine

1H NMR(CDCl₃) d 7.06(s,2H), 6.14(s,1H), 4.24(d,1H), 4.4-4.65(m,5H), 2.19(s,3H), 2.14(s,3H), 2.10(s,6H), 1.8(m,1H), 1.65(m,1H), 1.25(t,3H), 1.03(t,3H) ppm.

[3,6-Dimethyl-2-(2,4,6-trimethoxy-phenoxy)-pyridin-4-yl]-(1-methoxymethyl-propyl)-amine

1H NMR(CDCl₃) d 6.20(s,2H), 6.08(s,1H), 3.80(s,3H), 3.73(s,6H), 3.8(m,2H), 3.39(m,1H), 3.36(s,3H), 2.23(brs,3H), 2.10(s,3H), 1.74(m,1H), 1.59(m,1H), 0.969t,3H) ppm.

25 [2-(4-Bromo-2,6-dimethyl-phenoxy)-3-methoxy-6-methyl-pyridin-4-yl]-(1-ethyl-propyl)-amine

1H NMR(CDCl₃) d 7.18(s,2H), 6.09(s,1H), 4.43(d,1H), 3.89(s,3H), 3.25(m,1H), 2.10(s,9H), 1.4-1.8(m,4H), 0.95(t,6H) ppm.

(1-Ethyl-propyl)-[3-methoxy-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-amine

30 1H NMR(CDCl₃) d 6.85(s,2H), 6.07(s,1H), 4.44(m,1H), 3.89(s,3H), 3.23(m,1H), 2.27(s,3H), 2.09(s,6H), 2.08(s,3H), 1.65(m,2H), 1.45(m,2H), 0.93(m,6H) ppm.

[2-(4-Chloro-2,6-dimethyl-phenoxy)-6-methyl-3-propyl-pyridin-4-yl]-(1-ethyl-propyl)-amine

[2-(4-Bromo-2,6-dimethyl-phenoxy)-6-methyl-3-propyl-pyridin-4-yl]-(1-ethyl-propyl)-amine

- 1H NMR(CDCl₃) d 7.03(s,2H), 6.13(s,1H), 3.8(m,1H), 3.74(s,2H), 3.38(m,1H), 2.15(s,3H), 2.05(s,6H), 1.50-1.7(m,4H), 0.97(t,6H) ppm.
- (1-Ethyl-propyl)-[6-methyl-3-propyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-amine
- [2-(2,4-Dichloro-6-methyl-phenoxy)-3-methoxy-6-methyl-pyridin-4-yl]-[1-ethyl-propyl]-amine
- 5 amine
- 1H NMR(CDCl₃) 7.24(d,1H), 7.1(d,1H), 6.1(s,1H), 4.47(d,1H), 3.9(s,3H), 3.22(m,1H), 2.12(s,3H), 2.08(s,3H), 1.4-1.7(m,4H), 0.9(t,6H) ppm.
- [2-(4-Chloro-2,6-dimethyl-phenoxy)-3-methoxy-6-methyl-pyridin-4-yl]-[1-ethyl-propyl]-amine
- 10 1H NMR(CDCl₃) 7.02(s,2H), 6.07(s,1H), 4.44(brs,1H), 3.8-3.95(m,3H), 3.23(m,1H), 2.09(s,6H), 2.08(s,3H), 1.4-1.7(m,4H), 0.93(t,6H) ppm.
- [2-(4-Chloro-2,6-dimethyl-phenoxy)-3-methoxy-6-methyl-pyridin-4-yl]-[1-methoxymethyl-propyl]-amine
- 15 1H NMR(CDCl₃) d 7.02(s,2H), 6.11(s,1H), 4.71(d,1H), 3.88(s,3H), 3.45(m,2H), 3.37(s,3H), 2.10(s,3H), 2.09(s,6H), 1.73(m,1H), 1.59(m,1H), 0.98(m,3H) ppm.
- [2-(2,4-Dichloro-6-methyl-phenoxy)-3-methoxy-6-methyl-pyridin-4-yl]-[1-methoxymethyl-propyl]-amine
- 20 1H NMR (CDCl₃) d 7.1-7.25(m,2H), 6.13(s,1H), 4.74(d,1H), 3.91(s,3H), 3.47(m,1H), 3.39(m,2H), 3.37(s,3H), 2.14(s,3H), 2.10(s,3H), 1.78(m,1H), 1.59(m,1H), 0.98(t,3H) ppm.
- [2-(4-Chloro-2-methoxy-phenoxy)-3-methoxy-6-methyl-pyridin-4-yl]-[1-methoxymethyl-propyl]-amine
- 25 1H NMR (CDCl₃) d 6.8-7.0(m,3H), 6.17(s,1H), 4.76(d,1H), 3.82(s,3H), 3.75(s,3H), 3.3-3.5(m,3H), 3.35(s,3H), 2.19(s,3H), 1.73(m,1H), 1.56(m,1H), 0.96(t,3H) ppm.
- [2-(3-Chloro-2,6-dimethoxy-phenoxy)-3-methoxy-6-methyl-pyridin-4-yl]-[1-methoxymethyl-propyl]-amine
- 30 1H NMR(CDCl₃) d 7.12(d,1H), 6.64(d,1H), 6.12(s,1H)< 4.73(d,1H), 3.88(s,3H), 3.78(s,3H), 3.70(s,3H), 3.3-3.5(m,3H), 3.35(s,3H), 2.11(s,3H), 1.5-1.8(m,2H), 0.96(t,3H) ppm.
- (1-Methoxymethyl-propyl)-[3-methoxy-6-methyl-2-(2,4,6-trimethoxy-phenoxy)-pyridin-4-yl]-amine
- 35 1H NMR(CDCl₃) d 6.19(s,2H), 6.10(s,1H), 4.75(m,1H), 3.87(s,3H), 3.80(s,3H), 3.73(s,6H), 3.3-3.5(m,2H), 3.35(s,3H), 2.17(s,3H), 1.78(m,1H), 1.5(m,1H), 0.96(t,3H) ppm.
- [3-Methoxy-2-(4-methoxy-2,6-dimethyl-phenoxy)-6-methyl-pyridin-4-yl]-[1-ethoxymethyl-propyl]-amine
- 1H NMR(CDCl₃) d 6.59(s,2H), 6.10(s,1H), 4.70(d,1H), 3.89(s,3H), 3.77(s,3H), 3.48(m,1H), 3.39(m,2H), 3.37(s,3H), 2.11(s,3H), 2.10(s,6H), 1.74(m,1H), 1.57(m,1H), 0.98(t,3H) ppm.

[2-(4-Chloro-2,6-dimethyl-phenoxy)-3-ethoxy-6-methyl-pyridin-4-yl]-[1-methoxymethyl-propyl]-amine

1H NMR(CDCl₃) d 7.07(s,2H), 6.16(s,1H), 4.82(d,1H), 4.20(q,2H), 3.54(m,1H), 3.43(m,2H), 3.42(s,3H), 2.15(s,3H), 2.13(s,6H), 1.5-1.9(m,2H), 1.439t,3H), 1.02(t,3H) ppm.

5 Example 48

2-[2-(4-Chloro-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridin-4-(S)-ylamino]-butan-1-ol

To a solution of [1-(tert-butyl-dimethyl-silyloxyethyl)-propyl]-[2-(4-chloro-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridin-4-yl]-amine in dry THF was added 1M tetrabutylammonium fluoride in THF at room temperature. The mixture was stirred at room temperature for 2 hr, quenched with water, extracted with ethyl acetate. The organic layer was separated, dried and concentrated to dryness. The residue was purified by Biotage using 15% ethyl acetate in hexane as eluent to give the title compound as a white solid. 1H NMR(CDCl₃) d 7.06(s,2H), 6.18(s,1H), 4.04(d,1H), 3.74(m,1H), 3.69(m,1H), 3.53(m,1H), 2.18(s,3H), 2.16(s,3H), 2.10(s,6H), 1.6-1.8(m,2H), 1.04(t,3H) ppm.

15 The following compounds were prepared by the method analogous to that in the preceding paragraph, starting with the corresponding tert-butyl-dimethyl-silyloxyethyl derivative with tetrabutylammonium fluoride.

2-[3-Methoxy-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-(S)-ylamino]-butan-1-ol

1H NMR (CDCl₃) d 6.85(s,2H), 6.15(s,1H), 4.57(d,1H), 3.91(s,3H), 3.72(m,1H), 20 3.61(m,1H), 3.41(m,1H), 2.27(s,3H), 2.10(s,3H), 2.07(s,6H), 1.5-1.8(m,3H), 0.98(t,3H) ppm.

2-[2-(4-Chloro-2,6-dimethyl-phenoxy)-3-methoxy-6-methyl-pyridin-4-ylamino]-butan-1-ol

1H NMR(CDCl₃) d 7.02(s,2H), 6.16(s,1H), 4.60(d,1H), 3.91(s,3H), 3.71(m,1H), 3.61(m,1H), 3.40(m,1H), 2.10(s,3H), 2.08(s,6H), 1.8(brs,1H), 1.71(m,1H), 1.68(m,1H), 25 0.99(t,3H) ppm.

4-[4-(1-Hydroxymethyl-propylamino)-3-methoxy-6-methyl-pyridin-2-yloxy]-3,5-dimethyl-benzonitrile

1H NMR(CDCl₃) d 7.35(s,2H), 6.19(s,1H), 4.7(brs,1H), 3.88(s,3H), 3.731(m,1H), 3.64(m,1H), 3.43(m,1H), 2.14(m,9H), 1.8(brs,1H), 1.71(m,1H), 1.58(m,1H), 0.99(t,3H) ppm.

30 Example 49

3-[2-(4-Chloro-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridin-4-ylamino]-pentan-2-ol

The title compound was prepared by Dess Martin oxidation of 2-[2-(4-chloro-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridin-4-(S)-ylamino]-butan-1-ol methylene chloride at room temperature, followed by Gringard reaction using methyl magnesium bromide in THF. 1H NMR(CDCl₃) d 7.07(s,2H), 6.18(s,1H), 4.3(brs,1H), 4.0(m,1H), 3.32(m,1H), 2.22(s,3H), 2.17(s,3H), 2.11(s,6H), 1.6-1.8(m,2H), 1.30(d,3H), 1.01(t,3H) ppm.

Example 502-[2-Methyl-6-(2,4,6-trimethyl-phenoxy)-pyridin-4-ylamino]-butan-1-ol

The title compound was prepared as an oil by heating 2-(2,4,6-trimethyl-phenoxy)-4-(S)-(1-hydroxymethyl-propylamino)-6-methyl-nicotinic acid in 160°C until all starting material
5 were consumed. Anal. For C₁₉H₂₆N₂O₂ H₂O calc. C, 68.65; H, 8.49; N, 8.42; found C, 69.04;
H, 8.14; N, 8.91

Example 51(1-Ethyl-prop-2-ynyl)-[2-methyl-6-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-amine

The title compound was prepared by the method analogous to that in Example 163.
10 1H NMR(CDCl₃) d 6.89(s,2H), 6.12(d,1H), 5.41(d,1H), 3.9-4.2(m,2H), 2.37s,3H),
2.30(s,3H), 2.27(m,1H), 1.76(m,2H), 1.05(t,3H) ppm.

Example 522-(4-Bromo-2,6-dimethyl-phenoxy)-4-(1-ethyl-propylamino)-6-methyl-pyridin-3-ol

To a solution of [2-(4-bromo-2,6-dimethyl-phenoxy)-3-methoxy-6-methyl-pyridin-4-yl]-
15 (1-ethyl-propyl)-amine in methylene chloride was added BBr₃ at 0°C and stirred for hr. The mixture was quenched with water and extracted with chloroform. The organic layer was separated, dried, and concentrated to give the title compound. 1H NMR(CDCl₃) d 7.20(s,2H),
6.12(s,1H), 4.77(d,1H), 3.27(m,1H), 2.13(s,3H), 2.10(s,6H), 1.4-1.8(m, 4H), 0.97(t,6H) ppm.

The following compounds were prepared by the method analogous to that in the
20 preceding paragraph, starting with an appropriate [2-(substituted phenoxy)-3-methoxy-6-methyl-pyridin-4-yl]-(alkyl)-amine with BBr₃ or BCl₃.

4-(1-Ethyl-propylamino)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-3-ol

1H NMR(CDCl₃) d 6.85(s,2H), 6.10(s,1H), 5.12(brs,1H), 4.21(m,1H), 3.27(m,1H),
2.28(s,3H), 2.09(s,9H), 1.5-1.8(m,4H), 0.96(m,6H) ppm.
25 4-(S)-(1-Hydroxymethyl-propylamino)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-3-ol

1H NMR (CDCl₃) d 6.85(s,2H), 6.17(s,1H), 5.13(brs,1H), 4.28(d,1H), 3.73(m,1H),
3.60(m,1H), 3.50(m,1H), 2.27(s,3H), 2.12(s,3H), 2.07(s,6H), 1.75(brs,1H), 1.5-1.7(m,2H),
0.99(t,3H) ppm.
30 2-(4-Chloro-2,6-dimethyl-phenoxy)-4-(1-hydroxymethyl-propylamino)-6-methyl-pyridin-3-ol

1H NMR(CDCl₃) d 7.032(s,2H), 6.10(s,1H), 5.2(brs,1H), 4.35(brs,1H), 3.71(m,1H),
3.61(m,1H), 3.40(m,1H), 2.07(s,9H), 1.8(brs,1H), 1.71(m,1H), 1.60(m,1H), 0.99(m,3H) ppm.

35 2-(4-Chloro-2,6-dimethyl-phenoxy)-4-(1-ethyl-propylamino)-6-methyl-pyridin-3-ol
1H NMR(CDCl₃) d 7.02(s,2H), 6.10(s,1H), 5.02(brs,1H), 4.22(brs,1H), 3.25(brs,1H),
2.08(brs,9H), 1.62(m,2H), 1.52(m,2H), 0.95(brs,6H) ppm.

Example 53

Chloro-acetic acid 4-(1-ethyl-propylamino)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-3-yl ester

The title compound was prepared by reacting 4-(1-ethyl-propylamino)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-3-ol with chloroacetyl chloride /triethylamine in THF at 0°C to rt. 1H NMR(CDCl₃) δ 6.84(s,2H), 6.15(s,1H), 4.3(s,2H), 4.0(d,1H), 3.3(m,1H), 2.28(s,3H), 2.17(s,3H), 2.08(s,6H), 1.6-1.7(m,4H), 0.9(t,6H) ppm.

Example 54

2-(4-Chloro-2,6-dimethyl-phenoxy)-4-[(1-ethyl-propyl)-methyl-amino]-6-methyl-pyridin-3-ol

1H NMR(CDCl₃) δ 7.03(s,2H), 6.25(s,1H), 5.4(brs,1H), 3.93(m,1H), 2.70(s,3H), 2.12(s,3H), 2.08(s,6H), 1.55(m,4H), 0.89(t,6H) ppm.

Example 55

[4-(1-Ethyl-propylamino)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-3-yl]-acetonitrile

1H NMR(CDCl₃) δ 6.87(s,2H), 6.13(s,1H), 3.83(d,1H), 3.79(S,2H), 3.38(m,1H), 2.30(s,3H), 2.27(s,3H), 2.21(s,6H), 1.4-1.8(m,4H), 1.00(t,6H) ppm.

Example 56

4-(1-Ethyl-propylamino)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridine-3-carbaldehyde

1H NMR(CDCl₃) δ 10.52(s,1H), 9.26(d,1H), 6.89(s,2H), 6.11(s,1H), 3.42(m,1H), 2.31(s,3H), 2.15(s,3H), 2.11(s,6H), 1.45-1.75(m,4H), 0.97(t,6H) ppm.

Example 57

(1-Ethyl-propyl)-[3-[(1-ethyl-propylimino)-methyl]-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-amine

1H NMR(CDCl₃) δ 10.33(d,1H), 8.94(s,1H), 6.89(s,2H), 6.10(s,1H), 3.41(m,1H), 2.86(m,1H), 2.99(s,3H), 2.14(s,3H), 2.10(s,6H), 1.4-1.89m,8H), 0.94(t,6H), 0.87(t,6H) ppm.

Example 58

2-[4-(1-Ethyl-propylamino)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-3-ylmethyl]-malonic acid dimethyl ester

To a solution of dimethylmalonate (60 mg, 0.44 mmol) and 60% NaH in oil (20 mg, 0.44 mmol) in dry THF was added [3-Chloromethyl-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-1-ethyl-propyl-amine hydrogen chloride (50 mg, 0.146 mmol) at room temperature for 1 hr. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was separated, dried and concentrated to dryness. The residue was purified through silica gel column chromatography to give the title compound as a clear oil. 1H

NMR (CDCl_3) δ 6.88(s,2H), 6.03(s,1H), 4.85(m,1H), 4.03(t,1H), 3.73(s,6H), 3.26(m,1H), 3.18(d,2H), 2.30(s,3H), 2.13s,3H), 2.07(s,6H), 1.5-1.8(m,4H), 0.97(t,6H)ppm.

Example 59

- 5 2-[4-(1-Ethyl-propylamino)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-3-ylmethyl]-malonic acid diisopropyl ester

The title was prepared by the method analogous to that in Example 581. ^1H NMR (CDCl_3) δ 6.87(s,2H), 6.03(s,1H), 5.10(m,2H), 4.90(d,1H), 3.94(t,1H), 3.31(m,1H), 3.16(d,2H), 2.30(s,3H), 2.13s,3H, 2.08(s,6H), 1.5-1.8(m,4H), 1.1-1.3(two sets of d, 6H), 0.97(t,6H)ppm.

Example 60

- 10 4-(1-Ethyl-propoxy)-6-methyl-3-nitro-2-(2,4,6-trimethyl-phenoxy)-pyridine

To a mixture of 2-chloro-4-(1-ethyl-propoxy)-6-methyl-3-nitro-pyridine (500 mg, 1.93 mmol) and 2,4,6-trimethylphenol (289 mg, 2.13 mmol) in dry THF was added potassium t-butoxide. The resulting mixture was stirred at rt. overnight. The mixture was quenched with water, brine and extracted 3 times with ethyl acetate. The organic layer was separated, dried (MgSO_4) and concentrated to dryness. After silica gel column chromatography purification, the title compound was obtained as a light yellow crystal, mp 106-109°C. Anal. For $\text{C}_{20}\text{H}_{26}\text{N}_2\text{O}_4$ calc. C, 67.02; H, 7.31; N, 7.82; found, C, 67.34; H, 7.40; N, 7.42.

Example 61

- 20 4-(1-Ethyl-propoxy)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-3-ylamine

A mixture of 4-(1-ethyl-propoxy)-6-methyl-3-nitro-2-(2,4,6-trimethyl-phenoxy)-pyridine (150 mg, 0.418 mmol) and 10%Pd/C (23 mg) in ethanol was hydrogenated at 50 psi for 15 hours. An additional 10Pd/C was added and the resulting mixture was hydrogenated for an additional 24 hr. The mixture was filtered through celite and the filtrate was concentrated to dryness to give 200 mg of the crude material. After column chromatography, 25 the title compound was prepared as a the corresponding HCl salt as a white solid, mp 96-98°C.

Example 62

- 20 [4-(1-Ethyl-propoxy)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-3-yl]-dimethyl-amine

To a solution of 4-(1-ethyl-propoxy)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-3-ylamine in dry THF was added lithium bis(trimethylsilyl)amide at -78°C. After stirring at -78°C for 10 minutes, an excess of methyl iodide was added. The title compound was isolated after quenching with water and extracting with ethyl acetate. The crude material was purified by silica gel column chromatography to give the title compound as a tan foam.

Example 63N-[4-(1-Ethyl-propoxy)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-3-yl]-succinamic acid

- A mixture of 4-(1-ethyl-propoxy)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-3-ylamine (100mg, 0.304 mmol), succinic anhydride 31mg,0.304 mmol) and triethylamine in methylene chloride was stirred at rt. overnight. The mixture was quenched with water, and extracted with methylene chloride. The organic layer was separated, dried and concentrated to give a solid. The title compound was isolated as a white crystal after silica gel column chromatography.
- 10 ^1H NMR(CDCl_3) d 6.90(brs,1H), 6.84(s,2H), 6.37(s,1H), 4.2(m,1H), 2.6-2.8(m,4H), 2.28(s,3H), 2.22(s,3H), 2.03(s,6H), 1.69(m,4H), 0.94(t,6H) ppm.

Example 644-(1-Ethyl-propoxy)-3,6-dimethyl-2-[3-(2,4,6-trimethyl-pyridinoxy)]-pyridine

- To a solution of 3-pentanol (0.11 ml) in dry THF was added sodium hydride (60% in oil, 20 mg). After stirring for 5 min, a solution of 4-chloro-2,5-dimethyl-6-[3-(2,4,6-trimethyl-pyridinoxy)]-pyridine (92 mg, 0.332 mmol) in THF was added. DMSO was added and the resulting mixture was heated at 130°C oil bath overnight. The mixture was quenched with water, brine and extracted 3 times with ethyl acetate. The organic layer was separated, dried (MgSO_4) and concentrated to dryness. After silica gel column chromatography purification, the title compound was obtained as a clear oil. ^1H NMR (CDCl_3) d 6.88 (s,1H), 6.37(s,1H), 4.21(m,1H), 2.5(s,3H), 2.29(s,3H), 2.19(s,3H), 2.18(s,3H), 2.07(s,3H), 1.70(m,4H), 0.98(t,6H) ppm. The oil was prepared as the corresponding HCl salt to give a white solid (63 mg).

- The title compounds of the following Examples 65 and 66 were prepared by the methods analogous to that in Example 64, starting with an appropriate 6-alkyl-4-chloro-or 25 bromo-3-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridine with 3-pentanol/ NaH :

Example 656-Ethyl-4-(1-ethyl-propoxy)-3-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridine

1 ^1H NMR(CDCl_3) d 6.87(s,2H), 6.28(s,1H), 4.20(m,1H), 2.46(q,2H), 2.30(s,3H), 2.20(s,3H), 2.07(s,6H), 1.72(m,4H), 1.05(t,3H), 0.99(t,6H) ppm.

30 Example 66

4-(1-Ethyl-propoxy)-2-(4-fluoro-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridine

colorless oil. Anal. For $\text{C}_{20}\text{H}_{26}\text{FNO}_2$ calc. C, 72.48; H, 7.91; N, 4.23; found C, 72.39; H, 7.77; N, 4.10.

Example 67[4-(1-Ethyl-propoxy)-3,6-dimethyl-pyridin-2-yl]-(2,4,6-trimethyl-phenyl)-amine

To a solution of 4-(1-ethyl-propoxy)-6-methyl-2-(2,4,6-trimethyl-phenylamino)-nicotinic acid (240 mg, 0.673 mmol) in dry THF was added lithium aluminum hydride and aluminum chloride. The resulting mixture was heated at reflux for 3 hours. The mixture was quenched with 0.1ml water and 0.1ml 2N NaOH , then quenched with water and ethyl acetate. The organic layer was separated, dried and concentrated to give 250 mg of brown oil. After silica gel column chromatography, 170 mg(78%) of the title compound was obtained which was prepared as a HCl salt as a white solid, mp. 132-133°C. 1H NMR(CDCl₃) d 6.87(s,2H), 10 6.09(s,1H), 5.399brs,1H), 4.13(m,1H), 2.27(s,3H), 2.22(s,3H), 2.15(s,6H), 1.98(s,3H), 1.67(m,4H), 0.94(t,6H) ppm.

Example 68[4-(1-Ethyl-propoxy)-6-methyl-2-(2,4,6-trimethyl-phenylamino)-pyridin-3-yl]-methanol

To a solution of 4-(1-ethyl-propoxy)-6-methyl-2-(2,4,6-trimethyl-phenylamino)-nicotinic acid (100 mg, 0.281 mmol) in dry THF was added BH₃.DMS. The resulting mixture was heated at reflux overnight. The mixture was quenched with dilute HCl and stirred for 30 minutes, adjusted pH to 7.5-8.5, then extracted with ethyl acetate. The organic layer was separated, dried and concentrated to give 100 mg of brown oil. After silica gel column chromatography, 91 mg(95%) of the title compound was obtained as a white foam. Anal. For 20 C₂₁H₃₀N₂O₂.1/2H₂O cal. C, 71.76; H, 8.89; N, 7.97; found: C, 71.97; H, 8.90; N, 7.69.

Example 69[4-(1-Ethyl-propoxy)-6-methyl-2-(2,4,6-trimethyl-phenylamino)-pyridin-3-yl]-oxo-acetonitrile

The title compound was prepared by reacting [4-(1-ethyl-propoxy)-6-methyl-2-(2,4,6-trimethyl-phenylamino)-pyridin-3-yl]-methanol with thionyl chloride in benzene, concentrated to dryness, followed by reacting with diethylaluminum cyanide. After standard workup procedure and silica gel column chromatography, the title compound was obtained as a yellow crystal, mp. 108-110°C.

1H NMR(CDCl₃) d 8.57(s,1H), 6.97(s,2H), 6.37(s,1H), 4.46(m,1H), 2.35(s,3H), 30 2.34(s,3H), 2.09(s,6H), 1.6-1.8(m,4H), 0.99(t,6H) ppm.

Example 70[4-(1-Ethyl-propoxy)-6-methyl-2-(2,4,6-trimethyl-phenylamino)-pyridin-3-yl]-imidazol-1-yl-methanone

To a solution of 4-(1-ethyl-propoxy)-6-methyl-2-(2,4,6-trimethyl-phenylamino)-nicotinic acid (250 mg, 0.701 mmol) in 2ml of DMF was added carbonyldiimidazole (190 mg, 1.19 mmol) and the resulting mixture was stirred at room temperature overnight. After standard

workup procedure and silica gel column chromatography, 260 mg(91.2%) of the title compound was obtained as a golden crystal, mp. 120-122°C, Anal. For $C_{24}H_{30}N_4O_2 \cdot 1/4H_2O$ calc: C, 70.13; H, 7.48; N, 13.63; Found: C, 70.06; H, 7.69; N, 13.37.

Example 71

- 5 2-[4-(1-Ethyl-propoxy)-6-methyl-2-(2,4,6-trimethyl-phenylamino)-pyridin-3-yl]-propan-2-ol

The title compound was prepared by reacting [4-(1-ethyl-propoxy)-6-methyl-2-(2,4,6-trimethyl-phenylamino)-pyridin-3-yl]-imidazol-1-yl-methanone with an excess MeMgBr in THF at rt. After standard workup procedure and silica gel column chromatography, the title 10 compound was obtained as a tan solid, mp. 81-83°C; Anal. For $C_{22}H_{30}N_2O_2 \cdot 1.5H_2O$ calc.: C, 69.49; H, 9.38; N, 7.04; found: C, 69.49; H, 9.27; N, 6.86

Example 72

- 2-[4-(1-Ethyl-propoxy)-6-methyl-2-(2,4,6-trimethyl-phenylamino)-pyridin-3-ylmethyl]-malonic acid dimethyl ester

15 The title compound was prepared by reacting [4-(1-ethyl-propoxy)-6-methyl-2-(2,4,6-trimethyl-phenylamino)-pyridin-3-yl]-methanol with thionyl chloride in benzene, concentrated to dryness, followed by reacting with methyl malonate/NaH in DMSO. After standard workup procedure and silica gel column chromatography, the title compound was obtained as a solid, mp. 96-98°C; Anal. For $C_{26}H_{36}N_2O_5 \cdot 1/3H_2O$ calc.: C, 67.51; H, 7.99; N, 6.04; found: C, 67.48; 20 H, 7.99; N, 6.02.

Example 73

- 3-[4-(1-Ethyl-propoxy)-6-methyl-2-(2,4,6-trimethyl-phenylamino)-pyridin-3-yl]-propionic acid

Hydrolysis of 2-[4-(1-ethyl-propoxy)-6-methyl-2-(2,4,6-trimethyl-phenylamino)-pyridin-25 3-ylmethyl]-malonic acid dimethyl ester with phosphoic/water at reflux to give the title compound as a white foam. Anal. For $C_{23}H_{32}N_2O_3 \cdot 3/4H_2O$ calc.: C, 69.40; H, 8.48; N, 7.04; found: C, 69.17; H, 8.62; N, 6.90.

Example 74

- [3-Aminomethyl-4-(1-ethyl-propoxy)-6-methyl-pyridin-2-yl]-(2,4,6-trimethyl-phenyl)-amine

The title compound was prepared by reacting [4-(1-ethyl-propoxy)-6-methyl-2-(2,4,6-trimethyl-phenylamino)-pyridin-3-yl]-methanol with thionyl chloride in benzene, concentrated to dryness, followed by reacting with NH₃(g) at room temperature. After standard workup procedure and silica gel column chromatography, the title compound was obtained as a 35 golden oil (80%), Anal. For $C_{21}H_{31}N_3O$. calc.: C, 73.86; H, 9.15; N, 12.3; found: C, 73.50; H, 9.25; N, 11.39.

Example 752-Chloro-N-[4-(1-ethyl-propoxy)-6-methyl-2-(2,4,6-trimethyl-phenylamino)-pyridin-3-ylmethyl]-acetamide

The title compound was prepared by acylation of 3-aminomethyl-4-(1-ethyl-propoxy)-5-methyl-pyridin-2-yl]-[2,4,6-trimethyl-phenyl]-amine with chloroacetyl chloride. After standard workup procedure and silica gel column chromatography, the title compound was obtained as an off-white crystal, mp. 142-144°C; Anal. For $C_{23}H_{32}ClN_3O_2$. calc.: C, 66.09; H, 7.72; N, 10.05; found: C, 65.81; H, 7.64; N, 9.86.

Example 76[3-Dimethylaminomethyl-4-(1-ethyl-propoxy)-6-methyl-pyridin-2-yl]-[2,4,6-trimethyl-phenyl]-amine hydrochloride salt

The title compound was prepared by reacting [4-(1-ethyl-propoxy)-6-methyl-2-(2,4,6-trimethyl-phenylamino)-pyridin-3-yl]-methanol with thionyl chloride in benzene, concentrated to dryness, followed by reacting with dimethylamine at room temperature. After standard work-up procedure and silica gel column chromatography, the title compound was obtained as an oil. The corresponding HCl salt was prepared as a white solid, mp. 85-88°C; Anal. For $C_{23}H_{35}N_3O \cdot 2HCl \cdot 1.5 H_2O$ calc.: C, 58.83; H, 8.588; N, 8.94; found: C, 58.32; H, 8.5327; N, 8.64.

Example 77Dithiocarbonic acid O-ethyl ester S-[4-(1-ethyl-propoxy)-6-methyl-2-(2,4,6-trimethyl-phenylamino)-pyridin-3-ylmethyl] ester

The title compound was prepared by reacting [4-(1-ethyl-propoxy)-6-methyl-2-(2,4,6-trimethyl-phenylamino)-pyridin-3-yl]-methanol with thionyl chloride in benzene, concentrated to dryness, followed by reacting with NaSCSOEt at room temperature. After standard work-up procedure and silica gel column chromatography, the title compound was obtained as a white solid, mp. 55-57°C; Anal. For $C_{24}H_{34}N_2O_2S_2$. calc.: C, 64.54; H, 7.67; N, 6.27; found: C, 64.67; H, 7.78; N, 6.26.

Example 784-(1-Ethyl-propoxy)-6-methyl-2-(2,4,6-trimethyl-phenylamino)-nicotinamide

The title compound was prepared by reacting 4-(1-ethyl-propoxy)-6-methyl-2-(2,4,6-trimethyl-phenylamino)-nicotinic acid with thionyl chloride in benzene, concentrated to dryness, followed by reacting with $NH_3(g)$ at room temperature. After standard work-up procedure and silica gel column chromatography, the title compound was obtained as an oil. The corresponding HCl salt was prepared as an off-white solid, mp 185-187°C; Anal. For $C_{21}H_{29}N_3O_2$. calc.: C, 70.96; H, 8.22; N, 11.82; found: C, 71.30; H, 8.33; N, 11.78.

Example 794-(1-Ethyl-propoxy)-6-methyl-2-(2,4,6-trimethyl-phenylamino)-nicotinonitrile

The title compound was prepared by reacting 4-(1-ethyl-propoxy)-6-methyl-2-(2,4,6-trimethyl-phenylamino)-nicotinamide with triphosgen/triethylamine in THF. mp 105-107°C, 1H NMR(CDCl₃) d 6.90(s,2H), 6.26(brs,1H), 6.05(s,1H), 4.24(m,1H), 2.28(s,3H), 2.25(s,3H), 2.17(s,6H), 1.72(m,4H), 0.97(t,6H) ppm.

Example 804-(1-Ethyl-propoxy)-6,N,N-trimethyl-2-(2,4,6-trimethyl-phenylamino)-nicotinamide

The title compound was prepared by reacting 4-(1-ethyl-propoxy)-6-methyl-2-(2,4,6-trimethyl-phenylamino)-nicotinic acid with thionyl chloride in benzene, concentrated to dryness, followed by reacting with dimethylamine at room temperature. After standard work-up procedure and silica gel column chromatography, the title compound was obtained as an oil. The corresponding HCl salt was prepared as a white solid, mp. 197-200°C; Anal. For C₂₃H₃₃N₃O₂.H₂O. calc.: C, 63.07; H, 8.28; N, 9.59; found: C, 63.24; H, 8.07; N, 9.61.

Example 81[4-(1-Ethyl-propoxy)-6-methyl-2-(2,4,6-trimethyl-phenylamino)-pyridin-3-yl]-acetonitrile

The title compound was prepared by reacting [4-(1-ethyl-propoxy)-6-methyl-2-(2,4,6-trimethyl-phenylamino)-pyridin-3-yl]-methanol with thionyl chloride in benzene, concentrated to dryness, followed by reacting with potassium cyanide in DMSO at room temperature. After standard work-up procedure and silica gel column chromatography, the title compound was obtained as a pale orange solid, mp. 112-115°C, 1H NMR(CDCl₃) d 6.9(s,2H), 6.14(s,1H), 5.6(brs,1H), 4.22(m,1H), 3.49(s,2H), 2.28(s,3H), 2.22(s,3H), 2.16(s,6H), 1.71(m,4H), 0.95(t,6H) ppm.

Example 82[2-(4-Bromo-2,6-dimethyl-phenylamino)-4-(1-ethyl-propoxy)-6-methyl-pyridin-3-yl]-methanol

To a solution of 4-(1-ethyl-propoxy)-6-methyl-2-(4-bromo-2,6-dimethyl-phenylamino)-nicotinic acid (130 mg, 0.309 mmol) in dry THF was added BH₃.DMS. The resulting mixture was heated at reflux overnight. The mixture was quenched with dilute HCl and stirred for 30 min, adjusted pH to 7.5-8.5, then extracted with ethyl acetate. The organic layer was separated, dried and concentrated to give 100 mg of brown oil. After silica gel column chromatography, 110mg(87.3%) of the title compound was obtained as a white semi-solid. 1H NMR(CDCl₃) d 7.25(s,2H), 6.85(brs,1H), 4.8(brs,2H), 4.18(m,1H), 2.2(s,3H), 2.07(s,6H), 1.7(m,4H), 0.95(t,6H) ppm.

Example 83[2-(4-chloro-2,6-dimethyl-phenylamino)-4-(1-ethyl-propoxy)-6-methyl-pyridin-3-yl]-methanol

To a solution of 4-(1-ethyl-propoxy)-6-methyl-2-(4-chloro-2,6-dimethyl-phenylamino)-nicotinic acid in dry THF was added BH₃.DMS. The resulting mixture was heated at reflux overnight. The mixture was quenched with dilute HCl and stirred for 30 minutes, adjusted pH to 7.5-8.5, then extracted with ethyl acetate. The organic layer was separated, dried and concentrated to give a brown oil. After silica gel column chromatography, the title compound was obtained as a green oil. 1H NMR(CDCl₃) δ 7.02(s,2H), 6.83(brs,1H), 4.78(s,2H), 4.14(m,1H), 2.2(s,3H), 2.13(s,6H), 1.66(m,4H), 0.93(t,6H) ppm.

Example 84[2-(2,4-Dichloro-phenylamino)-4-(1-ethyl-propoxy)-6-methyl-pyridin-3-yl]-methanol

To a solution of 4-(1-ethyl-propoxy)-6-methyl-2-(2,4-dichloro-phenylamino)-nicotinic acid in dry THF was added BH₃.DMS. The resulting mixture was heated at reflux overnight. The mixture was quenched with dilute HCl and stirred for 30 min, adjusted pH to 7.5-8.5, then extracted with ethyl acetate. The organic layer was separated, dried and concentrated to give a golden oil. After silica gel column chromatography, the title compound was obtained as a golden oil. 1H NMR(CDCl₃) δ 8.44(d,1H), 8.18(s,1H), 7.32(d,1H), 7.179d,1H), 6.28(s,1H), 4.82(s,2H), 4.21(m,1H), 2.42(s,3H), 1.6-1.8(m,4H), 0.94(t,6H) ppm.

Example 85[2-(2,4-Dimethoxy-phenylamino)-4-(1-methoxymethyl-propoxy)-6-methyl-pyridin-3-yl]-methanol

The title compound was prepared by a method analogous to that described for Example 84, starting with the corresponding nicotinic acid with BH₃.DMS. 1H NMR(CDCl₃) δ 6.91(d,1H), 6.50(m,2H), 5.91(s,1H), 4.42(m,1H), 4.281(s,2H), 3.79(s,3H), 3.76(s,3H), 3.56(m,2H), 3.40(s,3H), 2.33(s,3H), 1.6-1.8(m,2H), 1.02(t,3H) ppm.

Example 86[4-(1-Ethyl-propylamino)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-3-yl]-imidazol-1-yl-methanone

The title compound was prepared by a method analogous to that described for Example 70, starting with the corresponding nicotinic acid with carbonyldiimidazole. 1HNMR(CDCl₃) δ 8.1(s,1H), 7.52(s,1H), 7.05(s,1H), 6.78(s,2H), 6.17(s,1H), 5.97(d,1H), 3.3(m,1H), 2.23(s,3H), 2.18(s,3H), 2.00(s,6H), 1.4-1.7(m,4H), 0.93(t,6H) ppm.

Example 871-[4-(1-Ethyl-propylamino)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-3-yl]-ethanone

The title compound was prepared by reacting [4-(1-Ethyl-propylamino)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-3-yl]-imidazol-1-yl-methanone with methylmagnesium bromide/ethyl ether in methylene chloride. ^1H NMR(CDCl_3) d 9.7(d,1H), 6.88(s,2H), 6.10(s,1H), 3.32(m,1H), 2.73(s,3H), 2.31(s,3H), 2.10(s,3H), 2.09(s,6H), 1.5-1.7(m,4H), 0.95(t,6H) ppm.

Example 88

10 (1-Ethyl-propyl)-[6-methyl-3-propyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-amine
 ^1H NMR(CDCl_3) d 6.84(s,2H), 6.04(s,1H), 3.81(d,1H), 3.31(m,1H), 2.56(t,2H), 2.27(s,3H), 2.12(s,3H), 2.04(s,6H), 1.4-1.7(6H), 1.02(t,3H), 0.93(t,6H) ppm.

Example 89

15 2-[4-(1-Ethyl-propylamino)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-3-ylmethyl]-2-methyl-malonic acid dimethyl ester

The title compound was prepared by a method analogous to that described for Example 72. ^1H NMR(CDCl_3) 6.87(s,2H), 6.01(s,1H), 5.05(m,1H), 3.70(s,6H), 3.4(s,2H), 3.3(m,1H), 2.27(s,3H), 2.12(s,3H), 2.07(s,6H), 1.4-1.7(m,4H), 1.48(s,3H), 0.949(t,6H) ppm.

Example 90

20 [4-(1-Ethyl-propoxy)-6-methyl-pyridin-2-yl]-[2,4,6-trimethyl-phenyl]-amine

The title compound was prepared by decarboxylation of the corresponding nicotinic acid at 160°C oil bath. mp. 98-100°C; Anal. For $\text{C}_{20}\text{H}_{28}\text{N}_2\text{O}$ calc. C, 76.88; H, 9.03; N, 8.97; found: C, 76.97; H, 9.21; N, 8.99.

The following title compounds of Examples 204 and 205 were prepared by reacting of 25 3-methoxy-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridine-4-carbaldehyde with alkyl-magnesium bromide in THF:

Example 91

2-Ethyl-1-[3-methoxy-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-butan-1-ol
 ^1H NMR(CDCl_3) 6.87(s,2H), 6.72(s,1H), 4.90(t,1H), 4.00(s,3H), 2.29(s,3H), 30 2.19(s,3H), 2.06(s,6H), 1.2-1.6(m,5H), 0.92(t,3H), 0.88(t,3H) ppm.

Example 92

1-[3-Methoxy-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-2-methyl-butan-1-ol
 ^1H NMR(CDCl_3) 6.88(s,2H), 6.74(s,1H), 5.00(m,1H), 4.00(s,3H), 2.29(s,3H), 2.19(s,3H), 2.06(s,6H), 1.4-1.9(m,3H), 0.992(t,3H), 0.989(d,3H) ppm.

Example 931-[3,6-Dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-propan-1-ol

To a -78°C solution of 4-bromo-3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridine in dry THF was added nBuLi and stirred at that temperature for 20 minutes. Excess 5 propionaldehyde was added and stirred for 2 hours at -78°C. The mixture was quenched with water, extracted with ethyl acetate. The organic layer was washed with brine, dried and concentrated. After column chromatography, an off-white solid was obtained, mp. 119-120°C. ^1H NMR(CDCl₃) d 6.86(s,3H), 4.90(m,1H), 2.281(s,3H), 2.28(s,3H), 2.21(s,3H), 2.02(s,6H), 1.65-1.8(m,2H), 1.00(t,3H) ppm.

10

Example 944-(1-Methoxy-propyl)-3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridine

The title compound was prepared by reaction of 1-[3,6-Dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-propan-1-ol with sodium hydride, followed by quenching with methyl iodide. ^1H NMR(CDCl₃) d 6.87(s,2H), 6.74(s,1H), 4.33(m,1H), 3.25(s,3H), 2.28(s,3H), 15 2.27(s,3H), 2.21(s,3H), 2.03(s,6H), 1.6-1.8(m,2H), 0.94(t,3H) ppm.

Example 954-(1-Ethoxy-propyl)-3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridine

The title compound was prepared by reaction of 1-[3,6-Dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-propan-1-ol with sodium hydride, followed by quenching with ethyl iodide.

20 ^1H NMR(CDCl₃) d 6.86(s,2H), 6.77(s,1H), 4.41(m,1H), 3.22-3.45(m,2H), 2.28(s,3H), 2.27(s,3H), 2.21(s,3H), 2.03(s,6H), 1.6-1.8(m,2H), 1.20(t,3H), 0.95(t,3H) ppm.

Example 964-(1-Allyloxy-propyl)-3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridine

25 The title compound was prepared by reaction of 1-[3,6-Dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-propan-1-ol with sodium hydride, followed by quenching with allyl bromide.

30 ^1H NMR(CDCl₃) d 6.87(s,2H), 6.78(s,1H), 5.93(m,1H), 5.1-5.3(m,2H), 4.48(m,1H), 3.95(m,1H), 3.76(m,1H), 2.29(s,3H), 2.26(s,3H), 2.21(s,3H), 2.03(s,6H), 1.6-1.8(m,2H), 0.96(t,3H) ppm.

Example 974-(1-Butoxy-propyl)-3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridine

35 The title compound was prepared by reacting of 1-[3,6-Dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-propan-1-ol with sodium hydride, followed by quenching with butyl iodide.

1H NMR(CDCl₃) d 6.86(s,2H), 6.76(s,1H), 4.37(m,1H), 3.35(m,1H), 3.25(m,1H), 2.28(s,3H), 2.26(s,3H), 2.20(s,3H), 2.03(s,6H), 1.6-1.8(m,2H), 1.5-1.65(m,2H), 1.3-1.5(m,2H), 0.96(t,3H), 0.89(t,3H) ppm.

The title compounds of the following Examples 98 through 102 were prepared by a method analogous to that described in Example 93 starting with an appropriate 4-bromo-2-(substituted-phenoxy)-pyridine derivative with nBuLi, followed by quenching with an appropriate aldehyde.

Example 98

10 1-ol
 one racemate 1H NMR(CDCl₃) d 7.28(d,1H), 7.14(d,1H), 6.80(s,1H), 4.92(d,1H), 4.00(s,3H), 2.21(s,3H), 2.13(s,3H), 1.3-1.65(m,5H), 0.93(t,3H), 0.87(t,3H) ppm.

15 The other racemate 1H NMR (CDCl₃) d 7.18(s,1H), 7.08(d,1H), 6.74(d,1H), 5.17(m,1H), 3.93(s,3H), 2.75(m,1H), 2.1-2.25(m,1H), 2.16(s,3H), 2.13(s,3H), 1.6-1.8(m,2H), 1.0-1.3(m,2H), 0.93(t,3H), 0.72(t,3H) ppm.

Example 99

1-[3,6-Dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-2,2,2-trifluoro-ethanol

mp. 134-139°C, Anal. For C₁₈H₂₀F₃NO₂ calc.: C, 63.71; H, 5.94; N, 4.13; found: C, 63.59; H, 6.00; N, 4.02.

20 Example 100

1-[2-(4-Chloro-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridin-4-yl]-2,2,2-trifluoro-ethanol
 1H NMR(CDCl₃) d 6.979s,2H), 6.19(s,1H), 2.14(s,6H), 2.06(s,6H) ppm.

Example 101

[2-(4-Chloro-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridin-4-yl]-pyridin-2-yl-methanol

25 1H NMR(CDCl₃) d 8.61(d,1H), 7.71(m,1H), 7.30(m,1H), 7.10(m,1H), 7.03(s,2H), 6.70(s,1H), 6.03(s,1H), 2.37(s,3H), 2.16(s,3H), 2.03(s,6H), ppm.

Example 102

1-[2-(4-Chloro-2,6-dimethyl-phenoxy)-3-methoxy-6-methyl-pyridin-4-yl]-2-ethyl-butanol-1-ol
 30 1H NMR(CDCl₃) d 7.05(s,2H), 6.759s,1H), 4.90(t,1H), 3.98(s,3H), 2.19(s,3H), 2.06(s,6H), 2.13(d,1H), 1.25-1.65(m,5H), 0.92(t,3H), 0.87(t,3H) ppm.

The title compounds of the following Examples 103 through 106 were prepared by oxidation of the corresponding alcohol with Dess Martin reagent in DMSO/methylene chloride or pyridinium chlorochromate in methylene chloride.

Example 1031-[3,6-Dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-propan-1-one

mp. 82-85.5°C, Anal. For $C_{19}H_{25}NO_2$ calc.: C, 76.74; H, 7.80; N, 4.71; Found: C, 76.61; H, 7.94; N, 4.66.

5

Example 1041-[2-(4-Chloro-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridin-4-yl]-2,2,2-trifluoroethanone

1H NMR($CDCl_3$) d 7.06(s,2H), 6.99(s,1H), 2.42(s,3H), 2.30(s,3H), 2.03(s,6H) ppm.

10

Example 105[2-(4-Chloro-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridin-4-yl]-pyridin-2-yl-methanone

1H NMR($CDCl_3$) d 8.72(d,1H), 8.17(d,1H), 7.95(m,1H), 7.52(m,1H), 7.05(s,2H), 6.75(s,1H), 2.25(s,3H), 2.22(s,3H), 2.07(s,6H) ppm.

15

Example 1061-[2-(4-Chloro-2,6-dimethyl-phenoxy)-3-methoxy-6-methyl-pyridin-4-yl]-2-ethyl-butane-1-one

1H NMR($CDCl_3$) d 7.05(s,2H), 6.67(s,1H), 3.98(s,3H), 3.09(m,1H), 2.61(s,3H), 2.06(s,6H), 1.76(m,2H), 1.51(m,2H), 0.92(t,6H) ppm.

20

Example 1074-(1-Ethoxy-2,2,2-trifluoro-ethyl)-3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridine

The title compound was prepared by reacting the corresponding alcohol with NaH, followed by quenching with ethyl iodide.

1H NMR($CDCl_3$) d 6.92(s,1H), 6.87(s,2H), 4.92(m,1H), 3.60(m2H), 2.349s,3H), 2.29(s,3H), 2.26(s,3H), 2.03(s,6H), 1.26(t,3H) ppm.

25

The title compounds of the following Examples 108 through 109 were prepared by

reacting of the corresponding ketone with alkyl lithium or alkyl magnesium.

30

Example 1082-[3,6-Dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-butan-2-ol

1H NMR($CDCl_3$) d 6.86(m,3H), 2.48(s,3H), 2.28(s,3H), 2.21(s,3H), 2.02(s,6H), 1.8-2.1(m,2H), 1.61(s,3H), 0.84(t,3H) ppm.

Example 1093-[3,6-Dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-pentan-3-ol

1H NMR($CDCl_3$) d 6.87(s,1H), 6.86(s,2H), 2.43(s,3H), 2.28(s,3H), 2.21(s,3H), 2.0-2.2(m,2H), 2.02(s,6H), 1.7-1.9(m,2H), 1.69(brs,1H), 0.8(t,6H) ppm.

Example 1101-[2-(4-Chloro-2,6-dimethyl-phenoxy)-3-hydroxy-6-methyl-pyridin-4-yl]-2-ethyl-butan-1-one

The title compound was prepared by reacting 1-[2-(4-Chloro-2,6-dimethyl-phenoxy)-3-methoxy-6-methyl-pyridin-4-yl]-2-ethyl-butan-1-one with BBr_3 or BCl_3 in THF or methylene chloride.

1H NMR (CDCl_3) d 7.04(s,2H), 7.01(s,1H), 3.26(m,1H), 2.24(s,3H), 2.08(s,6H), 1.80(m,2H), 1.63(m,2H), 0.91(t,6H) ppm.

Example 1114-(1-Ethyl-propylamino)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-nicotinamide

To a solution of 4-(1-ethyl-propylamino)-6-methyl-2-(2,4,6-trimethyl-phenoxy)nicotinic acid in anhydrous methylene chloride was added thionyl chloride. After stirring for 1 hr, the reaction mixture was concentrated to dryness. The residue was dissolved in dry THF and $\text{NH}_3(\text{g})$ was bubbled in. The reaction mixture was quenched with water and extracted with ethyl acetate. The organic layer was separated, dried and concentrated to give a light yellow solid. The solid was purified through silica gel column chromatography using 1% methanol in chloroform as eluent to give the title compound as a white solid, mp. 85-88°C. 1H NMR(CDCl_3) d 9.69(brs,1H), 8.01(brs,1H), 6.87(s,2H), 6.11(s,1H), 5.48(brs,1H), 3.31(m,1H), 2.29(s,3H), 2.10(s,3H), 2.07(s,6H), 1.60(m,4H), 0.95(t,6H) ppm.

The title compounds of the following Examples 112 through 118 were prepared by a method analogous to that described in the preceding paragraph, starting with the corresponding nicotinic acid or pyrimidine-5-carboxylic derivative and quenching with an appropriate nucleophile.

Example 1124-(1-Ethyl-propylamino)-6,N-dimethyl-2-(2,4,6-trimethyl-phenoxy)-nicotinamide

1H NMR(CDCl_3) d 9.8(brs,1H), 8.21(brs,1H), 6.88(s,2H), 6.11(s,1H), 3.31(m,1H), 2.92(d,3H), 2.30(s,3H), 2.10(s,3H), 2.07(s,6H), 1.60(m,4H), 0.95(t,6H) ppm.

Example 1132-(4-Chloro-2,6-dimethyl-phenoxy)-4-(S)-(1-hydroxymethyl-propylamino)-6-methyl-nicotinamide

1H NMR(CDCl_3) d 9.7(d,1H), 7.9(brs,1H), 7.0(s,2H), 6.2(s,1H), 5.6(brs,1H), 3.7(m,1H), 3.66(m,1H), 3.54(m,1H), 2.07(s,3H), 2.068(s,3H), 2.06(s,3H), 1.7(m,1H), 1.6(m,1H), 0.99(t,3H) ppm.

Example 1142-(4-Chloro-2,6-dimethyl-phenoxy)-4-(S)-(1-hydroxymethyl-propylamino)-6-methyl-nicotinic acid hydrazide

1H NMR(CDCl₃) d 9.15(s,1H), 7.04(s,2H), 6.23(s,1H), 3.6-3.8(m,2H), 3.53(m,1H),
5 2.08(s,6H), 2.05(s,3H), 2.04(s,3H), 1.5-1.8(m,2H), 1.01(t,3H) ppm.

Example 1152-(4-Chloro-2,6-dimethyl-phenoxy)-N-ethyl-4-(S)-(1-hydroxymethyl-propylamino)-6-methyl-nicotinamide

1H NMR(CDCl₃) d 9.74(d,1H), 8.12(s,1H), 7.05(s,2H), 6.23(s,1H), 3.5-3.8(m,3H),
10 3.43(m,2H), 2.06(s,9H), 1.8(brs,1H), 1.5-1.7(m,2H), 1.19(t,3H), 1.00(t,3H) ppm.

Example 1162-(4-Chloro-2,6-dimethyl-phenoxy)-4-(S)-(1-hydroxymethyl-propylamino)-6,N-dimethyl-nicotinamide

1H NMR(CDCl₃) d 9.80(d,1H), 8.12(s,1H), 7.04(s,2H), 6.22(s,1H), 3.5-3.8(m,3H),
15 2.93(d,3H), 2.06(s,9H), 1.8(brs,1H), 1.5-1.7(m,2H), 0.99(t,3H) ppm.

Example 1172-(4-Chloro-2,6-dimethyl-phenoxy)-N-cyclopentyl-4-(S)-(1-hydroxymethyl-propylamino)-6-methyl-nicotinamide

1H NMR(CDCl₃) d 9.69(d,1H), 8.13(d,1H), 7.04(s,2H), 6.22(s,1H), 4.35(m,1H), 3.4-
20 3.8(m,3H), 2.056(s,9H), 1.4-2.0(m, 10H), 0.99(t,3H) ppm.

Example 1182-(4-Chloro-2,6-dimethyl-phenoxy)-N-cyclopropylmethyl-4-(S)-(1-hydroxymethyl-propylamino)-6-methyl-nicotinamide

1H NMR(CDCl₃) d 9.71(d,1H), 8.24(s,1H), 7.05(s,2H), 6.23(s,1H), 3.5-3.8(m,3H),
25 3.27(t,2H), 2.08(s,6H), 2.07(s,3H), 1.8(brs,1H), 1.5-1.75(m,2H), 0.99(t,3H), 0.46(m,2H),
0.21(m,2H) ppm.

The title compounds of the following Examples 232 through 236 were prepared by a method analogous to that described for Example 224.

Example 1194-(1-Ethyl-propylamino)-6-methyl-2-(2,4,6-trimethyl-phenylamino)-nicotinamide

A brown solid, mp. 204-206°C.

Example 1204-(1-Ethyl-propoxy)-2-methyl-6-(2,4,6-trimethyl-phenylamino)-pyrimidine-5-carboxylic acid amide

5 Mp. 174-176°C; Anal. For $C_{20}H_{28}N_4O_2$ calc.: C, 67.39; H, 7.92; N, 15.72; found: C, 67.90; H, 8.19; N, 14.66. 1H NMR($CDCl_3$) d 7.95(s,1H), 6.89(s,2H), 5.58(s,1H), 5.4(m,1H), 2.28(s,3H), 2.25(s,3H), 2.15(s,6H), 1.75(m,4H), 0.96(t,6H) ppm.

Example 121

10 4-(1-Ethyl-propylamino)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-nicotinonitrile
 1H NMR($CDCl_3$) d 6.85(s,2H), 6.06(s,1H), 4.72(d,1H), 3.36(m,1H), 2.28(s,3H), 2.17(s,3H), 2.09(s,6H), 1.5-1.8(m,4H), 0.96(t,6H) ppm.

Example 122[4-(1-Ethyl-propoxy)-6-methyl-3-nitro-pyridin-2-yl]-[2,4,6-trimethyl-phenyl]-amine

15 The title compound was prepared by heating 2-bromo (or chloro)-4-(1-ethyl-propoxy)-6-methyl-3-nitro-pyridine with 2,4,6-trimethylaniline in DMSO at 130°C. The reaction mixture was quenched with water and extracted with ethyl acetate. The organic layer was separated, dried and concentrated to give crude material. The material was purified through silica gel column chromatography to give the title compound as a yellow solid. 1H NMR($CDCl_3$) d 8.52(s,1H), 6.92(s,2H), 6.12(s,1H), 4.31(m,1H), 2.32(s,3H), 2.24(s,3H), 2.18(s,6H), 1.77(m,4H), 1.01(t,6H) ppm.

Example 1234-(1-Ethyl-propoxy)-6-methyl-N2-(2,4,6-trimethyl-phenyl)-pyridine-2,3-diamine

20 The title compound was prepared by hydrogenation of the corresponding 3-nitro derivative with 10%Pd/C in ethanol at 50 psi. A pale gray solid was obtained in 97% yield, mp. 73-75°C. 1H NMR($CDCl_3$) d 6.89(s,2H), 6.18(s,1H), 4.22(m,1H), 3.2(brs,2H), 2.29(s,3H), 2.19(s,6H), 1.7(m,4H), 0.97(t,6H) ppm.

Example 1242-Chloro-N-[4-(1-ethyl-propoxy)-6-methyl-2-(2,4,6-trimethyl-phenylamino)-pyridin-3-yl]-acetamide

25 The title compound was prepared by acylation of 4-(1-ethyl-propoxy)-6-methyl-N2-(2,4,6-trimethyl-phenyl)-pyridine-2,3-diamine with chloroacetyl chloride, NEt_3 in THF at room temperature. A tan solid was isolated, mp. 79-82°C. Anal. For $C_{22}H_{30}ClN_3O_2$ calc. C, 65.41; H, 7.49; N, 10.40; found: C, 65.56; H, 7.62; N, 10.98.

Example 125N-Butyl-N-ethyl-6-methyl-3-nitro-N-(2,4,6-trimethyl-phenyl)-pyridine-2,4-diamine

35 A mixture of butyl-(2-chloro-6-methyl-3-nitro-pyridin-4-yl)-ethyl-amine (700 mg, 2.58 mmol) and 2,4,6-trimethylaniline in DMSO was heated in 140°C oil bath for overnight. An

additional 0.75 ml of 2,4,6-trimethylaniline was added and the resulting mixture was heated for an additional 48 hours. The mixture was quenched with water, brine and extracted 3 times with ethyl acetate. The organic layer was separated, dried ($MgSO_4$) and concentrated to dryness. After silica gel column chromatography purification, the title compound was obtained
5 as an oil.

Example 126

4-(1-Ethyl-propylamino)-6-methyl-2-(2,4,6-trimethyl-phenylamino)-nicotinic acid

The title compound was prepared by heating 2-chloro-4-(1-ethyl-propylamino)-6-methyl-nicotinic acid and trimethylaniline in the presence of potassium carbonate and copper
10 in DMF. The desired product was isolated by silica gel column chromatography using 5% methanol in chloroform as solvent to give a tan solid, mp. 130-135°C.

Example 127

4-(1-Ethyl-propylamino)-6-methyl-2-(2,4,6-trimethyl-phenylamino)-nicotinic acid methyl ester

A mixture of 2-chloro-4-(1-ethyl-propylamino)-6-methyl-nicotinic acid methyl ester, trimethylaniline, potassium carbonate, copper in DMF was heated at reflux. The mixture was quenched with ammonium chloride and stirred for 20 min, filtered through celite and washed with ethyl acetate. The filtrate was extracted with ethyl acetate. The organic layer was separated, dried and concentrated to dryness. The residue was purified through silica gel
20 column chromatography using 2% methanol in chloroform as eluent to give the title compound as a solid.

1H NMR($CDCl_3$) d 8.9(s,1H), 8.0(d,1H), 6.91(s,2H), 5.79(s,1H), 3.92(s,3H), 3.37(m,1H), 2.30(s,3H), 2.17(s,3H), 2.10(s,6H), 1.5-1.7(m,4H), 0.96(t,6H) ppm.

Example 128

N4-(1-Ethyl-propyl)-3,6-dimethyl-N2-(2,4,6-trimethyl-phenyl)-pyridine-2,4-diamine

The title compound was prepared by reduction of 4-(1-ethyl-propylamino)-6-methyl-2-(2,4,6-trimethyl-phenylamino)-nicotinic acid with 1M of lithium aluminium hydride in diethyl ether and aluminium trichloride at reflux. 1H NMR($CDCl_3$) 6.9(s,2H), 6.0(s,1H), 5.4(brs,1H), 3.6(d,1H), 3.3(m,1H), 2.32(s,3H), 2.2(s,3H), 2.15(s,6H), 1.4-1.7(m,4H), 1.0(t,6H) ppm.

Example 129

2-[4-(1-Ethyl-propylamino)-6-methyl-2-(2,4,6-trimethyl-phenylamino)-pyridin-3-ylmethyl]-malonic acid dimethyl ester

Mp. 136-138°C; Anal. For $C_{28}H_{37}N_3O_4$. 3/4 H_2O calc.: C, 66.57; H, 8.27; N, 8.96; found: C, 66.67; H, 7.95; N, 8.88.

Example 130[2-(4-Bromo-2,6-dimethyl-phenylamino)-4-(1-ethyl-propylamino)-6-methyl-pyridin-3-yl]-methanol

The title compound was prepared by reduction of the corresponding nicotinic acid derivative with BH₃.DMS in THF at reflux. Standard work-up procedure gave the title compound as a white foam. ¹H NMR(CDCl₃) 7.15(s,2H), 6.2(brs,1H), 5.92(s,1H), 4.47(m,1H), 4.43(s,2H), 3.25(m,1H), 2.17(s,3H), 2.10(s,6H), 1.58(m,2H), 1.47(m,2H), 0.90(t,6H) ppm.

Example 131N2-(2,4-Dichloro-phenyl)-N4-(1-ethyl-propyl)-3,6-dimethyl-pyridine-2,4-diamine

The title compound was prepared by a method analogous to that described for Example 33. ¹H NMR(CDCl₃) d 7.79(dd,1H), 7.30(d,1H), 7.10(dd,1H), 6.53(brs,1H), 6.13(s,1H), 3.79(d,1H), 3.2-3.4(m,1H), 2.36(s,3H), 1.92(s,3H), 1.4-1.6(m,4H), 0.93(t,6H) ppm.

Example 132[2-(2,4-Dichloro-phenylamino)-4-(1-ethyl-propylamino)-6-methyl-pyridin-3-yl]-methanol

The title compound was prepared by reduction of the corresponding nicotinic acid derivative with BH₃.DMS in THF at reflux. ¹H NMR(CDCl₃) d 7.22(d,1H), 7.07(d,1H), 7.00(d,1H), 6.10(s,1H), 5.7(brs,1H), 4.4(s,2H), 3.3 (m,1H), 2.35(s,3H), 2.02(s,3H), 1.4-1.6(m,4H), 0.92&0.91(two sets of t,6H) ppm.

Example 1332-[6-Methyl-3-nitro-2-(2,4,6-trimethyl-phenylamino)-pyridin-4-ylamino]-butan-1-ol

The title compound was prepared by heating 2-[6-methyl-3-nitro-2-chloro-pyridin-4-ylamino]-butan-1-ol with trimethylaniline in DMSO at 130°C. ¹H NMR(CDCl₃) d 9.38(brs,1H), 6.93(s,3H), 3.7-3.8(m,3H), 2.30(s,3H), 2.12(s,6H), 1.8(m,1H), 1.65(m,1H), 1.02(t,3H) ppm

Example 1342-[4-(1-Ethyl-propylamino)-2-methyl-6-(2,4,6-trimethyl-phenoxy)-pyrimidin-5-yl]-propionic acid ethyl ester

¹H NMR(CDCl₃) d 6.85(s,2H), 5.16(d,1H), 4.49(q,1H), 4.0-4.2(m,3H), 2.289(s,3H), 2.20(s,3H), 2.06(s,6H), 1.4-1.7(m,4H), 1.44(d,3H), 1.21(t,3H), 0.93(t,3H), 0.87(t,3H) ppm.

Example 135[3-Aminomethyl-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-[1-ethyl-propyl]-amine

The title compound was prepared by a method analogous to that described for Example 75. mp. 117-119°C; Anal. For C₂₁H₃₁N₃O. 1/3 H₂O calc.: C, 72.58; H, 9.18; N, 12.09; found: C, 72.93; H, 9.28; N, 12.02.

The following title compounds of Examples 136-138 were prepared by reacting [4-(1-ethyl-propylamino)-6-methyl-2-(4-halo-2,6-dimethyl-phenoxy)-pyridin-3-yl]-methanol with thionyl chloride in benzene, concentrated to dryness, followed by reacting with potassium cyanide in DMSO at room temperature.

Example 136

[2-(4-Bromo-2,6-dimethyl-phenoxy)-4-(1-ethyl-propylamino)-6-methyl-pyridin-3-yl]-acetonitrile

¹H NMR(CDCl₃) δ 7.2(s,2H), 6.1(S,1H), 3.82(d,1H), 3.7(s,2H), 3.34(m,1H), 2.1(s,3H), 2.03(s,6H), 1.45-1.7(m,4H), 0.99(t,6H) ppm.

Example 137

[2-(4-Chloro-2,6-dimethyl-phenoxy)-4-(1-ethyl-propylamino)-6-methyl-pyridin-3-yl]-acetonitrile hydrogen chloride

¹H NMR(CDCl₃) δ 7.08(s,2H), 6.2(s,1H), 4.92(d,1H), 3.45(m,1H), 2.71(s,3H), 2.549(m,2H), 2.14(s,6H), 1.7(m,2H), 1.40-1.6(m,4H), 0.95(t,6H) ppm.

15 Example 138

[6-(1-Ethyl-propoxy)-2-methyl-pyrimidin-4-yl]-(2,4,6-trimethyl-phenyl)-amine

MP. 149–151°C, Anal. For $C_{20}H_{26}N_4O$ calc.: C, 72.81; H, 8.68; N, 13.41; found: C, 72.70; H, 8.86; N, 13.14

Example 139

20 2-[2-(4-Chloro-2,6-dimethyl-phenoxy)-6-methyl-pyridin-4-(S)-ylamino]-butan-1-ol

The title compound was prepared by heating the corresponding nicotinic acid derivative at 160-170°C oil bath. ^1H NMR (CDCl_3) δ 7.05(s,2H), 6.09(s,1H), 5.35(s,1H), 4.43(s,1H), 3.68(m,1H), 3.64(m,1H), 3.29(m,1H), 2.30(s,3H), 2.09(s,6H), 1.60(m,1H), 1.47(m,1H), 0.89(t,3H) ppm.

Example 140

[3-Aminomethyl-2-(4-chloro-2,6-dimethyl-phenoxy)-6-methyl-pyridin-4-(S)-yl]-[1-chloromethyl-propyl]-amine

The title compound was prepared by reacting [2-[2-(4-chloro-2,6-dimethyl-phenoxy)-3-pyridin-4-(S)-ylamino]-butan-1-ol with thionyl chloride in benzene, concentrated to dryness, followed by reacting with NH₃(g) at room temperature. After standard workup procedure and silica gel column chromatography, the title compound was obtained. ¹H NMR(CDCl₃) δ 7.00(s,2H), 6.3(brs,1H), 6.07(s,1H), 4.0-4.2(m,2H), 3.9(brs,2H), 3.5-3.8(m,3H), 2.12(s,3H), 2.03(s,6H), 1.6-1.9(m,2H), 1.00(t,3H) ppm

The following title compounds of Examples 254 and 255 were prepared by reacting [2-[2-(4-chloro-2,6-dimethyl-phenoxy)-3-pyridin-4-(S)-ylamino]-butan-1-ol with thionyl chloride in benzene, concentrated to dryness, followed by reacting with an appropriate amine in THF

at room temperature. After standard workup procedure and silica gel column chromatography, the title compound was obtained.

Example 141

- 5 2-[2-(4-Chloro-2,6-dimethyl-phenoxy)-6-methyl-3-methylaminomethyl-pyridin-4-(S)-ylamino]-butan-1-ol

1H NMR(CDCl₃) d 7.01(s,2H), 6.14(s,1H), 4.55(brs,1H), 3.6-3.8(m,2H), 3.4(m,1H), 2.6(s,3H), 2.11(s,3H), 2.02(brs,6H), 1.65(m,2H), 0.97(t,3H)ppm.

Example 142

- 10 2-[3-Aminomethyl-2-(4-chloro-2,6-dimethyl-phenoxy)-6-methyl-pyridin-4-(S)-ylamino]-butan-1-ol

1H NMR(CDCl₃) d 6.999s,2H), 6.10(s,1H), 4.4.00(Abq,2H), 3.5-3.75(m,2H), 3.4(m,1H), 2.73(brs,4H), 2.08(s,3H), 2.00(s,6H), 1.58(m,4H), 0.94(t,3H) ppm.

The title compounds of the following Examples 143 through 149 were prepared by bromination or chlorination of 2-[2-(substituted-phenoxy)-6-methyl-pyridin-4-alkylamine with 15 NBS or NCS in methylene chloride or chloroform at room temperature.

Example 143

[3-Bromo-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-[1-ethyl-propyl]-amine

1H NMR(CDCl₃) d 6.85(s,2H), 6.04(s,1H), 4.62(d,1H), 3.33(m,1H), 2.27(s,3H), 2.13(s,3H), 2.08(s,6H), 1.5-1.7(m,2H), 0.95(t,3H) ppm.

- 20 Example 144

2-[3,5-Dibromo-2-(4-chloro-2,6-dimethyl-phenoxy)-6-methyl-pyridin-4-ylamino]-butan-1-ol

1H NMR(CDCl₃) d 7.02(s,2H), 4.34(m,1H), 3.6-3.8(m,2H), 2.30(s,3H), 2.05(s,6H), 1.5-1.8(m,2H), 0.98(t,3H) ppm.

- 25 Example 145

2-[3-Bromo-6-(4-chloro-2,6-dimethyl-phenoxy)-2-methyl-pyridin-4-(S)-ylamino]-butan-1-ol

1H NMR(CDCl₃) d 7.05(s,2H), 5.62(s,1H), 4.86(d,1H), 3.55-3.7(m,2H), 3.3(m,1H), 2.428(s,3H), 2.09(s,6H), 1.4-1.7(m,3H), 0.91(t,3H) ppm.

- 30 Example 146

2-[3-Bromo-2-(4-chloro-2,6-dimethyl-phenoxy)-6-methyl-pyridin-4-(S)-ylamino]-butan-1-ol

1H NMR(CDCl₃) d 7.02(s,2H), 6.14(s,1H), 4.81(d,1H), 3.6-3.8(m,2H), 3.45(m,1H), 2.12(s,3H), 2.08(s,6H), 1.5-1.8(m,2H), 1.00(t,3H) ppm.

Example 1472-[3-Chloro-2-(4-chloro-2,6-dimethyl-phenoxy)-6-methyl-pyridin-4-(S)-ylamino]-butan-1-ol

5 1H NMR(CDCl₃) d 7.02(s,2H), 6.18(s,1H), 4.76(d,1H), 3.6-3.8(m,2H), 3.45(m,1H),
 2.13(s,3H), 2.07(s,6H), 1.5-1.8(m,2H), 0.99(t,3H) ppm.

Example 1482-[3,5-Dichloro-2-(4-chloro-2,6-dimethyl-phenoxy)-6-methyl-pyridin-4-ylamino]-butan-1-ol

10 1H NMR(CDCl₃) d 7.03(s,2H), 4.34(m,1H), 3.6-3.8(m,2H), 2.40(s,3H), 2.05(s,6H),
 1.5-1.8(m,2H), 0.99(t,3H) ppm.

Example 1492-[3-Chloro-6-(4-chloro-2,6-dimethyl-phenoxy)-2-methyl-pyridin-4-(S)-ylamino]-butan-1-ol

15 1H NMR(CDCl₃) d 7.05(s,2H), 5.66(s,1H), 4.86(brs,1H), 3.5-3.8(m,2H), 3.3(m,1H),
 2.38(s,3H), 2.09(s,6H), 1.4-1.7(m,3H), 0.91(t,3H) ppm.

Example 1502-(4-Chloro-2,6-dimethyl-phenoxy)-4-(S)-(4-ethyl-2-oxo-oxazolidin-3-yl)-6-methyl-nicotinonitrile

The title compound was prepared by reacting with 2-(4-chloro-2,6-dimethyl-phenoxy)-4-(1-hydroxymethyl-propylamino)-6-methyl-nicotinic acid with triphosgene/NEt₃ in THF. 1H NMR(CDCl₃) d 7.18(s,1H), 7.06(s,2H), 5.00(m,1H), 4.64(t,1H), 4.23(dd,1H), 2.339s,3H), 2.08(s,6H), 1.5-1.8(m,2H), 0.949t,3H) ppm.

Example 1512-(2,4-Dimethoxy-phenylamino)-4-(1-methoxymethyl-propoxy)-6-methyl-nicotinic acid

25 1H NMR(CDCl₃) d 8.3(brs,1H), 6.5(m,3H), 6.26(s,1H), 4.66(m,1H), 3.92(s,3H),
 3.85(s,3H), 3.66(m,2H), 3.43(s,3H), 2.52(s,3H), 1.91(m,2H), 1.07(t,3H) ppm.

Example 1524-(1-Ethyl-propoxy)-2-methyl-6-(2,4,6-trimethyl-phenylamino)-pyrimidine-5-carbonitrile

30 1H NMR(CDCl₃) d 6.92(s,2H), 6.45(s,1H), 5.22(m,1H), 2.29(s,6H), 2.16(s,6H),
 1.70(m,4H), 0.93(t,6H) ppm.

Example 153N-(1-Ethyl-propyl)-2,5-dimethyl-N'-(2,4,6-trimethyl-phenyl)-pyrimidine-4,6-diamine

35 1H NMR(CDCl₃) d 8.9(s,1H), 6.85(s,2H), 4.95(d,1H), 4.21(m,1H), 2.5(s,3H),
 2.25(s,3H), 2.13(s,6H), 1.4-1.7(m,4H), 1.3(s,3H), 0.85(t,6H) ppm

Example 154

5-Chloro-N4-(1-ethyl-propyl)-2-methyl-N6-(2,4,6-trimethyl-phenyl)-pyrimidine-4,6-diamine

1H NMR(CDCl₃) d 6.85(s,2H), 6.0(s,1H), 4.0(m,1H), 4.2(m,1H), 2.3(s,3H), 2.22,(3H),
5 2.17(s,6H), 1.4-1.70(m,4H), 0.97(t,6H) ppm.

Example 155

5-Bromo-N-(1-ethyl-propyl)-2-methyl-N'-(2,4,6-trimethyl-phenyl)-pyrimidine-4,6-diamine

MP. 117-119°C, Anal. For C₁₉H₂₁BrN₄ calc.: C, 58.31; H, 6.95; N, 14.32; found: C,
10 58.43; H, 7.08; N, 14.23.

Example 156

4-(1-Ethyl-propylamino)-2-methyl-6-(2,4,6-trimethyl-phenylamino)-pyrimidine-5-carboxylic acid

1H NMR(CDCl₃) d 12.2(brs,1H), 11.1(brs,1H), 6.84(s,2H), 4.18(m,1H), 2.38(s,3H),
15 2.18(s,3H), 2.15(s,6H), 1.56(m,4H), 0.90(t,6H) ppm.

Example 157

[4-(Cyclopropylmethyl-propyl-amino)-2-methyl-6-(2,4,6-trichloro-phenylamino)-pyrimidin-5-yl]-methanol

1H NMR(CDCl₃) d 7.49(s,2H), 4.95(s,2H), 4.92(s,1H), 3.28(brs,4H), 2.359(s,3H),
20 1.54(m,2H), 0.95(m,1H), 0.81(t,3H), 0.44(m,2H), 0.19(m,2H) ppm.

Example 158

6-(1-Ethyl-propoxy)-2,N5,N5-trimethyl-N4-(2,4,6-trimethyl-phenyl)-pyrimidine-4,5-diamine

The title compound was prepared by methylation of 6-(1-ethyl-propoxy)-2-methyl-N4-(2,4,6-trimethyl-phenyl)-pyrimidine-4,5-diamine with lithium bis(trimethylsilyl)amide in THF, followed by quenching with methyl iodide. 1H NMR(CDCl₃) d 7.35(s,1H), 6.90(s,2H), 5.16(m,1H), 2.73(s,6H), 2.29(s,3H), 2.27(s,3H), 2.18(s,6H), 1.6-1.8(m,4H), 0.96(t,6H) ppm.

Example 159

[5-Bromo-6-(1-ethyl-propoxy)-2-methyl-pyrimidin-4-yl]-(2,4,6-trimethyl-phenyl)-amine

30 The title compound was prepared by reacting [5-bromo-6-(1-ethyl-propoxy)-2-methyl-pyrimidin-4-yl]-(2,4,6-trimethyl-phenyl)-amine with 3-pentanol/NaH in THF at reflux overnight. After standard work-up and purification, the title compound was obtained as a white solid, mp. 94-96°C. 1H NMR(CDCl₃) d 6.91(s,2H), 6.41(s,1H), 5.13(m,1H), 2.29(s,3H), 2.26,(3H), 2.17(s,6H), 1.70(m,4H), 0.95(t,6H) ppm.

Example 1604-(1-Ethyl-propoxy)-2-methyl-6-(2,4,6-trimethyl-phenylamino)-pyrimidine-5-carboxylic acid

To a solution of n-BuLi in THF was added a solution of [5-bromo-6-(1-ethyl-propoxy)-2-methyl-pyrimidin-4-yl]-[2,4,6-trimethyl-phenyl]-amine in THF at -78°C. After stirring for 10 minutes, CO₂(g) was added at -78°C and stirred at that temperature for 1 hour, then gradually warmed to room temperature. The resulting mixture was quenched with water and adjusted to pH 2 to 3 and extracted with chloroform. The organic layer was separated, dried and concentrated to dryness. The residue was purified through silica gel column chromatography to give the title compound as a solid, mp. 118-120°C, Anal. For C₂₀H₂₇N₃O₃ calc.: C, 67.20; H, 7.61; N, 11.76; found: C, 67.25; H, 7.87; N, 11.48.

Example 161[4-(1-Ethyl-propoxy)-2-methyl-6-(2,4,6-trimethyl-phenylamino)-pyrimidin-5-yl]-methanol

To a solution of 4-(1-ethyl-propoxy)-2-methyl-6-(2,4,6-trimethyl-phenylamino)-pyrimidine-5-carboxylic acid in dry THF was added BH₃.DMS. The resulting mixture was heated at reflux. The mixture was quenched with dilute HCl and stirred for 30 minutes, adjusted pH to 7.5-8.5, then extracted with ethyl acetate. The organic layer was separated, dried and concentrated to give a crude material. The crude material was purified through silica gel column chromatography to give the title compound as a solid, mp. 121-123°C, Anal. For C₂₀H₂₉N₃O₂ calc. C, 69.94; H, 8.51; N, 12.23; found: C, 69.73; H, 8.47; N, 11.99.

Example 162[6-(1-Ethyl-propoxy)-5-methoxymethyl-2-methyl-pyrimidin-4-yl]-[2,4,6-trimethyl-phenyl]-amine

The title compound was prepared by reacting [4-(1-ethyl-propoxy)-2-methyl-6-(2,4,6-trimethyl-phenylamino)-pyrimidin-5-yl]-methanol with NaH, followed by quenching with MeI. ¹H NMR(CDCl₃) δ 7.0(s,1H), 6.89(s,2H), 5.12(m,1H), 4.62(s,2H), 3.33(s,3H), 2.28(s,3H), 2.27(s,3H), 2.14(s,6H), 1.66(m,4H), 0.91(t,6H) ppm.

Example 163[5-Aminomethyl-6-(1-ethyl-propoxy)-2-methyl-pyrimidin-4-yl]-[2,4,6-trimethyl-phenyl]-amine

To a solution of [4-(1-ethyl-propoxy)-2-methyl-6-(2,4,6-trimethyl-phenylamino)-pyrimidin-5-yl]-methanol in anhydrous methylene chloride was added thionyl chloride. After stirring for 1 hour, the reaction mixture was concentrated to dryness. The residue was dissolved in dry THF and NH₃(g) was bubbled in. The reaction mixture was quenched with

water and extracted with ethyl acetate. The reaction was worked-up and purified by standard procedure to give the title compound.

1H NMR(CDCl₃) δ 8.50(s,1H), 6.88(s,2H), 5.08(m,1H), 3.97(s,2H), 2.279s,3H), 2.25(s,3H), 2.159s,6H), 1.74(brs,2H), 1.65(m,4H), 0.91(t,6H) ppm.

5

Example 1647-(1-Ethyl-propoxy)-5-methyl-3-(2,4,6-trimethyl-phenyl)-3H-imidazo[4,5-b]pyridin-2-ylamine

The title compound was prepared by reacting 4-(1-ethyl-propoxy)-6-methyl-N2-(2,4,6-trimethyl-phenyl)-pyridine-2,3-diamine with BrCN in acetonitrile at room temperature overnight. The mixture was quenched with water and adjusted to pH 8.0 with saturated sodium bicarbonate and extracted with ethyl acetate. The organic layer was separated, dried and concentrated to give crude material. The material was purified through silica gel column chromatography to give the title compound as a white solid, mp. 159-161°C. 1H NMR(CDCl₃) δ 7.05(s,2H), 6.5(s,1H), 4.6(m,1H), 4.3(m,2H), 2.45(s,3H), 2.35(s,3H), 2.0(s,6H), 1.7(m,4H), 1.0(t,6H) ppm.

15

Example 1657-(1-Ethyl-propoxy)-5-methyl-3-(2,4,6-trimethyl-phenyl)-3H-imidazo[4,5-b]pyridine

A mixture of 4-(1-ethyl-propoxy)-6-methyl-N2-(2,4,6-trimethyl-phenyl)-pyridine-2,3-diamine, trimethyl orthoformate, p-toluenesulfonic acid monohydrate in toluene was heated at reflux using Dean-Stark apparatus for 24 hours. The mixture was heated at reflux overnight. The mixture was quenched with water, sat. NaHCO₃, extracted with ethyl acetate. The organic layer was separated, dried (MgSO₄) and concentrated to dryness. After purification, the title compound was isolated. Anal. For C₂₁H₂₉N₃O·1/4H₂O calc. C, 73.76; H, 8.10; N, 12.29; found: C, 73.22; H, 7.96; N, 12.42.

25

Example 1667-(1-Ethyl-propoxy)-5-methyl-3-(2,4,6-trimethyl-phenyl)-1,3-dihydro-imidazo[4,5-b]pyridin-2-one

The title compound was prepared by reacting 4-(1-ethyl-propoxy)-6-methyl-N2-(2,4,6-trimethyl-phenyl)-pyridine-2,3-diamine with triphosgene, NEt₃ in THF at room temperature. A white solid was isolated, mp. 184-186°C. Anal. For C₂₁H₂₇N₃O₂ calc. C, 71.36; H, 7.70; N, 11.89; found: C, 71.09; H, 7.75; N, 11.63.

Example 1677-(1-Ethyl-propoxy)-1,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-1,3-dihydro-imidazo[4,5-b]pyridin-2-one

35

The title compound was prepared by reacting 7-(1-ethyl-propoxy)-5-methyl-3-(2,4,6-trimethyl-phenyl)-1,3-dihydro-imidazo[4,5-b]pyridin-2-one with lithium bis(trimethylsilyl)amide,

followed by quenching with methyl iodide. Mp. 151-153°C. Anal. For $C_{22}H_{29}N_3O_2$. 1/4H₂O calc. C, 71.03; H, 7.99; N, 11.30; found: C, 71.29; H, 8.01; N, 11.03.

Example 168

(1-Ethyl-propyl)-[5-methyl-3-(2,4,6-trimethyl-phenyl)-3H-imidazo[4,5-b]pyridin-7-yl]-

5 amine

A mixture of N-4-(1-ethyl-propyl)-6-methyl-N-2-(2,4,6-trimethyl-phenyl)-pyridine-2,3,4-triamine (250 mg, 0.77 mmol), trimethyl orthoformate (0.081 g, 0.766 mmol), p-toluenesulfonic acid monohydrate (0.01 g) in benzene was heated at reflux using Dean-Stark apparatus for 24 hours. Benzene was removed and toluene was added and an excess of 10 trimethyl orthoformate (0.084 ml) was added to the reaction mixture. The mixture was heated at reflux overnight. The mixture was quenched with water, sat. NaHCO₃, extracted with ethyl acetate. The organic layer was separated, dried (MgSO₄) and concentrated to dryness. After purification, the title compound was isolated as white crystals, mp 78-80°C.

Example 169

15 [2,5-Dimethyl-3-(2,4,6-trimethyl-phenyl)-3H-imidazo[4,5-b]pyridin-7-yl]-[1-ethyl-propyl]-amine

A mixture of N-4-(1-ethyl-propyl)-6-methyl-N-2-(2,4,6-trimethyl-phenyl)-pyridine-2,3,4-triamine (250 mg, 0.77 mmol), trimethyl orthoacetate (0.184 g, 1.532 mmol), p-toluenesulfonic acid monohydrate (0.01 g) in toluene was heated at reflux using Dean-Stark apparatus for 3 hours. The mixture was quenched with water, brine, extracted with ethyl acetate. The organic layer was separated, dried (MgSO₄) and concentrated to dryness. After purification, the title compound was obtained as a white crystal, mp 101-103°C. Anal. For $C_{22}H_{30}N_4$ calc. C, 75.39; H, 8.63; N, 15.98; found, C, 75.44; H, 8.95; N, 15.95.

Example 170

25 N7-(1-Ethyl-propyl)-5-methyl-3-(2,4,6-trimethyl-phenyl)-3H-imidazo[4,5-b]pyridine-2,7-diamine

The title compound was prepared by reacting N4-(1-ethyl-propyl)-6-methyl-N2-(2,4,6-trimethyl-phenyl)-pyridine-2,3,4-triamine with BrCN in acetonitrile at room temperature overnight. The mixture was quenched with water and adjusted to pH 8.0 with saturated sodium bicarbonate and extracted with ethyl acetate. The organic layer was separated, dried and concentrated to give crude material. The material was purified through silica gel column chromatography to give the title compound as a brown solid, mp. 158-160°C; Anal. For $C_{21}H_{29}N_5$ 1/4H₂O calc. C, 70.85; H, 8.35; N, 19.67; found: C, 71.07; H, 8.30; N, 19.63.

Example 1716-(1-Ethyl-propylamino)-2,7-dimethyl-9-(2,4,6-trimethyl-phenyl)-7,9-dihydro-purin-8-one

The title compound was prepared by methylation of 6-(1-ethyl-propylamino)-2-methyl-9-(2,4,6-trimethyl-phenyl)-7,9-dihydro-purin-8-one with lithium bis(trimethylsilyl)amide in THF, followed by quenching with methyl iodide. ^1H NMR(CDCl₃) d 6.98(s,2H), 4.45(d,1H), 4.3(m,1H), 3.7(s,3H), 2.4(s,3H), 2.3(s,3H), 2.1(s,6H), 1.5-1.8(m,4H), 1.0(t,6H) ppm.

Example 1726-(1-Ethyl-propoxy)-2,7-dimethyl-9-(2,4,6-trimethyl-phenyl)-7,9-dihydro-purin-8-one

The title compound was prepared by methylation of 6-(1-Ethyl-propoxy)-2-methyl-9-(2,4,6-trimethyl-phenyl)-7,9-dihydro-purin-8-one with lithium bis(trimethylsilyl)amide in THF, followed by quenching with methyl iodide. ^1H NMR(CDCl₃) d 7.00(s,2H), 5.31(m,1H), 3.66(s,3H), 2.479(s,3H), 2.33(s,3H), 2.06(s,6H), 1.79(m,4H), 1.01(t,6H) ppm.

Example 173[2-(4-Methoxy-2,6-dimethyl-phenoxy)-6-methyl-3-nitro-pyridin-4-yl]-[1-methoxymethyl-propyl]-amine

^1H NMR(CDCl₃) d 7.71(d,1H), 6.57(s,2H), 6.21(s,1H), 3.76(s,3H), 3.59(m,1H), 3.48(m,1H), 3.45(m,1H), 3.37(s,3H), 2.13(s,3H), 2.08(s,6H), 1.6-1.8(m,4H), 0.86(t,3H) ppm.

Example 174(1-Ethyl-propyl)-[2-(4-methoxy-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridin-4-yl]-amine

^1H NMR(CDCl₃) d 6.64(s,2H), 6.12(s,1H), 3.82(s,3H), 3.36(m,1H), 2.26(s,3H), 2.13(s,6H), 2.10(s,3H), 1.5-1.8m,4H), 0.99(t,6H).

Example 1752-[2-(4-Methoxy-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridin-4-ylamino]-butan-1-ol

^1H NMR(CDCl₃) d 6.64(s,2H), 6.13(s,1H), 4.10(m,1H), 3.76(s,3H), 3.7-3.8(m,21H), 3.57(m,1H), 2.21(s,3H), 2.19(s,6H), 2.12(s,3H), 1.6-1.8(m,2H), 1.04(t,3H) ppm.

Example 176sec-Butyl-[3-methoxy-2-(4-methoxy-2,6-dimethyl-phenoxy)-6-methyl-pyridin-4-yl]-amine

^1H NMR(CDCl₃) d 6.64(s,2H), 6.13(s,1H), 4.51(d,1H), 3.92(s,3H), 3.82(s,3H), 3.469m,1H), 2.18(s,3H), 2.15(s,6H), 1.60(m,2H), 1.26(d,3H), 1.00(t,3H) ppm.

Example 1772-(4-Chloro-2,6-dimethyl-phenoxy)-4-(4-ethyl-oxazolidin-3-yl)-3,6-dimethyl-pyridine

^1H NMR(CDCl₃) d 7.07(s,2H), 6.36(s,1H), 4.98(m,1H), 4.78(m,1H), 4.23(m,1H), 3.83(m,1H), 3.71(m,1H), 2.28(s,3H), 2.20(s,3H), 2.09(s,6H), 1.81(m,1H), 1.58(m,1H), 0.98(t,3H) ppm.

Example 1784-(4-Ethyl-oxazolidin-3-yl)-2-(4-methoxy-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridine

1H NMR(CDCl₃) d 6.65(s,2H), 6.36(s,1H), 4.98(m,1H), 4.77(m,1H), 4.23(m,1H),
 3.83(s,3H), 3.71(m,1H), 2.29(s,3H), 2.22(s,3H), 2.119(s,6H), 1.82(m,1H), 1.56(m,1H),
 5 0.99(t,3H) ppm

Example 1792-(4-Methoxy-2,6-dimethyl-phenoxy)-N%4&-(1-methoxymethyl-propyl)-6-methyl-pyridine-3,4-diamine

1H NMR(CDCl₃) d 6.64(s,2H), 6.16(s,1H), 4.3(m,1H), 3.82(s,3H), 3.6-3.8(m,2H),
 10 3.42(s,3H), 3.2(brs,2H), 2.18(s,3H), 2.13(s,6H), 1.6-1.8(m,2H), 1.03(t,3H) ppm.

Example 1803-[2-(4-Chloro-2,6-dimethyl-phenoxy)-3-hydroxymethyl-6-methyl-pyridin-4-ylamino]-pentan-2-ol

1H NMR(CDCl₃) d 7.01(s,2H), 6.16(s,1H), 5.19(d,1H), 4.94(m,2H), 3.88(m,1H),
 15 3.27(m,1H), 2.11(s,3H), 2.05(s,6H), 1.73(m,1H), 1.57(m,1H), 1.24(d,3H), 0.97(t,3H) ppm.

Example 1812-(4-Chloro-2,6-dimethyl-phenoxy)-4-(1-ethyl-2-oxo-propylamino)-6-methyl-nicotinic acid methyl ester

1H NMR(CDCl₃) d 8.63(d,1H), 7.01(s,2H), 5.90(s,1H), 3.95(m,1H), 3.90(s,3H),
 20 2.08(s,3H), 2.05(s,3H), 2.03(s,6H), 1.8-2.0(m,2H), 1.00(t,3H) ppm.

Example 1823-[2-(4-Chloro-2,6-dimethyl-phenoxy)-3-methoxymethyl-6-methyl-pyridin-4-ylamino]-pentan-2-ol

1H NMR(CDCl₃) d 7.08(s,2H), 6.21(s,1H), 5.40(brs,1H), 4.83(q,2H), 3.91(m,1H),
 25 3.40(s,3H), 3.33(m,1H), 2.20(s,3H), 2.10(s,6H), 1.78(m,1H), 1.58(m,1H), 1.29(d,3H),
 1.01(t,3H) ppm.

Example 1833-[2-(4-Methoxy-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridin-4-ylamino]-pentan-2-ol

1H NMR(CDCl₃) d 6.66(s,2H), 6.27(s,1H), 4.05(m,1H), 3.82(s,3H), 3.38(m,1H),
 30 2.35(s,3H), 2.21(s,3H), 2.14(s,6H), 1.6-1.9(m,2H), 1.30(m,3H), 1.01(t,3H) ppm.

Example 1844-sec-Butylamino-2-(4-methoxy-2,6-dimethyl-phenoxy)-6-methyl-nicotinic acid methyl ester

1H NMR(CDCl₃) d 8.01(d,1H), 6.58(s,2H), 6.06(s,1H), 3.85(s,3H), 3.77(s,3H),
 35 2.10(s,3H), 2.07(s,6H), 1.21(d,3H), 0.97(t,3H) ppm.

Example 1852-(4-Chloro-2,6-dimethyl-phenoxy)-4-(1-ethyl-2-hydroxy-2-methyl-propylamino)-6-methyl-nicotinic acid methyl ester

5 1H NMR(CDCl₃) d 8.28(d,1H), 7.06(s,2H), 6.32(s,1H), 3.92(s,3H), 3.41(m,1H),
2.14(s,3H), 2.12(s,6H), 1.91(m,1H), 1.44(m,1H), 1.33(s,3H), 1.30(s,3H0, 0.99(s,3H) ppm.

Example 186

10 4-(1-Hydroxymethyl-propylamino)-2-(4-methoxy-2,6-dimethyl-phenoxy)-6-methyl-nicotinic acid methyl ester
1H NMR(CDCl₃) d 8.13(d,1H), 6.63(s,2H), 6.21(s,1H), 3.91(s,3H0, 3.82(s,3H0,
3.81(m,2H), 3.59(m,1H), 2.16(s,3H), 2.12(s,6H), 1.6-1.859m,2H), 1.05(t,3H) ppm.

Example 1872-(4-Chloro-2,6-dimethyl-phenoxy)-4-(1-hydroxymethyl-3-methylsulfanyl-propylamino)-6-methyl-nicotinic acid methyl ester

A mixture of 2-(4-chloro-2,6-dimethyl-phenoxy)-4-chloro-6-methyl-nicotinic acid
15 methyl ester and L-methioninol in N-methyl-2-pyrdone (NMP) was heated in a 134°C oil bath
for 3 hr. Standard work-up procedure and purification provided the title compound. 1H
NMR(CDCl₃) d 8.25(d,1H), 7.02(s,2H), 6.30(s,1H), 3.85(s,3H), 3.6-3.9(m,3H), 2.5-2.7(m,2H),
2.14(s,3H), 2.10(s,3H), 2.06(s,6H), 1.8-2.1(m,2H)ppm.

Example 188

20 2-(4-Chloro-2,6-dimethyl-phenoxy)-6-methyl-4-(S)-(tetrahydro-furan-3-ylamino)-nicotinic acid methyl ester

To a solution of {3-[2-(4-chloro-2,6-dimethyl-phenoxy)-3-methoxycarbonyl-6-methyl-pyridin-4-ylamino]-4-hydroxy-butyl}-dimethyl-sulfonium iodide in dry THF was added t-BuOK
at -10°C. The mixture was stirred at -10°C until all starting material was consumed.
25 Standard work-up procedure and silica gel purification gave the title compound.

1H NMR(CDCl₃) d 8.25(d,1H), 7.01(s,2H), 6.05(s,1H), 4.11(m,1H), 3.9-4.1(m,2H),
3.8-3.9(m,1H), 3.86(s,3H), 3.73(m,1H), 2.2-2.4(m,1H), 2.11(s,3H), 2.05(s,6H), 1.95(m,1H)
ppm.

Example 189

30 {3-[2-(4-Chloro-2,6-dimethyl-phenoxy)-3-methoxycarbonyl-6-methyl-pyridin-4-ylamino]-4-hydroxy-butyl}-dimethyl-sulfonium iodide

A mixture of 2-(4-chloro-2,6-dimethyl-phenoxy)-4-(1-hydroxymethyl-3-methylsulfanyl-propylamino)-6-methyl-nicotinic acid methyl ester and MeI in EtOAc was heated at reflux in a
35 sealed tube. The mixture was concentrated to dryness and triturated with diethyl ether to give
the title compound. 1H NMR(CD₃OD) d 7.11(s,2H), 6.61(s,1H), 4.00(m,1H), 3.86(s,3H), 3.6-
3.9(m,3H), 2.95(d,6H), 2.5-2.7(m,2H), 2.22(s,3H), 2.07(s,6H), 1.8-2.1(m,2H)ppm.

Example 1904-(1-Hydroxymethyl-3-methylsulfanyl-propylamino)-2-(4-methoxy-2,6-dimethyl-phenoxy)-6-methyl-nicotinic acid methyl ester

5 1H NMR(CDCl₃) d 8.15(d,1H), 6.58(s,2H), 6.28(s,1H), 3.85(s,3H), 3.76(s,3H), 3.6-3.9(m,3H), 2.5-2.7(m,2H), 2.12(s,3H), 2.09(s,3H), 2.07(s,6H), 1.8-2.1(m,2H)ppm.

Example 191

10 1H NMR(CDCl₃) d 9.84(d,1H), 8.31(m,1H), 6.66(s,2H), 6.29(s,1H), 3.81(s,3H), 3.5-3.9(m,3H), 2.98(d,3H), 2.15(s,3H), 2.12(s,6H), 1.6-1.8(m,2H), 1.05(t,3H)ppm.

Example 1924-sec-Butylamino-2-(4-methoxy-2,6-dimethyl-phenoxy)-6,N-dimethyl-nicotinamide

15 1H NMR(CDCl₃) d 9.77(brs,1H), 8.22(brs,1H), 6.61(s,2H), 6.11(s,1H), 3.78(s,3H), 3.45(m,1H), 2.93(d,3H), 2.10(s,3H), 2.07(s,6H), 1.5-1.7(m,2H), 1.23(m,3H), 0.98(t,3H)ppm.

Example 1932-(4-Methoxy-2,6-dimethyl-phenoxy)-6-methyl-4-(tetrahydro-furan-3-ylamino)-nicotinic acid methyl ester

20 1H NMR(CDCl₃) d 8.28(d,1H), 6.63(s,2H), 6.09(s,1H), 4.15(m,1H), 3.98-4.1(m,2H), 3.8-3.98(m,1H), 3.90(s,3H), 3.81(s,3H), 3.76(m,1H), 2.32-2.36(m,1H), 2.19(s,3H), 2.11(s,6H), 1.95(m,1H) ppm.

Example 1944-sec-Butylamino-2-(4-methoxy-2,6-dimethyl-phenoxy)-6-methyl-nicotinamide

25 1H NMR(CDCl₃) d 9.74(ds,1H), 8.05(brs,1H), 6.65(s,2H), 6.16(s,1H), 5.55(brs,1H), 3.83(s,3H), 3.51(m,1H), 2.16(s,3H), 2.12(s,6H), 1.5-1.7(m,2H), 1.26(d,3H), 1.02(t,3H)ppm.

The following Examples 195-256 relate to other compounds of formula I of the invention, wherein R₄ is -COOCH₃:

The following title compounds of Examples 195-209 were prepared by the method analogous to that described in Example 13 starting with an a 4-chloro-2-(substituted-phenoxy)-6-methyl-nicotinic acid methyl ester and with an appropriate amine:

Example 1952-(4-Ethoxy-2,6-dimethyl-phenoxy)-4-(1-hydroxymethyl-3-methylsulfanyl-propylamino)-6-methyl-nicotinic acid methyl ester

30 1H NMR (CDCl₃) d 8.35(d, 1H), 6.60(s, 2H), 6.41(s, 1H), 4.03(q, 2H), 3.90(m, 1H), 3.86(s, 3H), 3.75(m, 2H), 2.60(, 2H), 2.21(s, 3H), 2.11(s, 3H), 2.09(s, 6H), 2.03(m, 1H), 1.88(m, 1H), 1.40(t, 1.39)ppm

Example 1964-(1-Hydroxymethyl-3-methylsulfanyl-propylamino)-2-[4-(2-methoxy-ethoxy)-2,6-dimethyl-phenoxy]-6-methyl-nicotinic acid methyl ester

5 1H NMR(CDCl₃) d 8.38(d, 1H), 6.64(s, 2H), 6.42(s, 1H), 4.10(m, 2H), 3.92(m, 1H),
 3.86(s, 3H), 3.73(m, 5H), 3.45(s, 3H), 2.60(m, 2H), 2.22(s, 3H), 2.13(s, 3H), 2.09(s, 6H),
 1.87(m, 2H)ppm

Example 1972-(2,6-Dimethyl-4-trifluoromethoxy-phenoxy)-4-(1-hydroxymethyl-3-methylsulfanyl-propylamino)-6-methyl-nicotinic acid methyl ester

10 1H NMR(CDCl₃) d 8.21 (br d, 1H, J=8 Hz), 6.91 (s, 2H), 6.28 (s, 1H), 3.87 (s, 3H),
 3.84 (m, 1H), 3.70-3.76 (m, 2H), 2.53-2.68 (m, 2H), 2.11 (m, 12H), 1.88-2.06 (m, 2H).

Example 1982-(4-Chloro-2,6-dimethyl-phenoxy)-4-(R)-(1-hydroxymethyl-3-methylsulfanyl-propylamino)-6-methyl-nicotinic acid methyl ester

15 C₂₁H₂₇CIN₂O₄S: MS: M+1 [439.2]

Example 1992-(4-Chloro-2,6-dimethoxy-phenoxy)-4-(1-hydroxymethyl-propylamino)-6-methyl-nicotinic acid methyl ester

20 1H NMR(CDCl₃) d 8.29 (d, 1H, J=8 Hz), 6.63 (s, 2H), 6.23 (s, 1H), 3.86 (s, 3H), 3.74
 (s, 6H), 3.69-3.72 (m, 1H), 3.62-3.66 (m, 1H), 3.52-3.58 (m, 1H), 2.83 (s, 1H), 2.13 (s, 3H),
 1.70-1.77 (m, 1H), 1.54-1.61 (m, 1H), 0.99 (t, 3H, J=7Hz)
 13C NMR(CDCl₃) d.169.75, 158.50, 153.43, 130.15, 106.96, 101.49, 64.67, 56.95,
 56.12, 56.05, 52.18, 46.05, 24.92, 10.67

Example 2002-(4-Chloro-2,6-dimethoxy-phenoxy)-4-(1-hydroxymethyl-3-methylsulfanyl-propylamino)-6-methyl-nicotinic acid methyl ester

25 1H NMR(CDCl₃) d 8.39 (br d, 1H, J= 7 Hz), 6.64 (s, 2H), 6.30 (s, 1H), 3.87 (s, 3H),
 3.75 (s, 6H), 3.36-3.39 (m, 1H), 2.84 (s, 1H), 2.53-2.70 (m, 2H), 2.35-2.39 (m, 1H), 2.14 (d,
 3H, J = 9 Hz), 1.94-2.07 (m, 2H), 1.79-1.92 (m, 2H) ppm.

30 APCI+ m/z = 471.2 (M+1), 473.2 (M+3)

Example 2012-(4-Chloro-2,6-dimethyl-phenoxy)-4-[(1-hydroxymethyl-propyl)-methyl-amino]-6-methyl-nicotinic acid methyl ester

Example 202

4-(1-Ethyl-propylamino)-2-(4-methoxy-2,6-dimethyl-phenoxy)-6-methyl-nicotinic acid methyl ester

APCI M+I [387.3], 1H NMR(CDCl₃)

5

Example 203

2-(2,6-Dimethyl-4-[1,3,4]oxadiazol-2-yl-phenoxy)-4-(1-ethyl-propylamino)-6-methyl-nicotinic acid methyl ester

1H NMR(CDCl₃) d 8.43 (s, 1H), 8.22 (br d, 1/2H), 7.80 (s, 2H), 6.12 (s, 1H), 3.88 (s, 3H), 3.3-3.4 (m, 1H), 2.15-2.2 (m, 9H), 1.5-1.7 (m, 4H), 0.967 (t, 6H, J=7 Hz)

10

13C NMR(CDCl₃) d.

APCI+ m/z =425.3 (M+1)

Example 204

2-(4-Chloro-2-methoxy-phenoxy)-4-(1-ethyl-propylamino)-6-methyl-nicotinic acid methyl ester

15

1H NMR(CDCl₃) d 8.14 (d, 1H, J=8 Hz), 6.90-7.26 (m, 3H), 6.14 (s, 1H), 3.82 (s, 3H), 3.77 (s, 3H), 3.32-3.73 (m, 1H), 2.17 (s, 3H), 1.49-1.67 (m, 4H), 0.94 (t, 6H, J=7 Hz) ppm.

20

1HNMR(CDCl₃) 8.21(d, 1H), 6.60(s, 2H), 6.30(s, 1H), 3.87(s, 3H), 3.78(s, 3H), 3.65(m, 3H), 2.17(s, 3H), 2.09(s, 6H), 1.75(m, 1H), 1.61(m, 1H), 1.01(t, 3H)ppm

25

APCI+ m/z =411 (M+1), 413 (M+3)

Example 206

2-(4-Chloro-2-fluoro-6-methoxy-phenoxy)-4-(1-ethyl-propylamino)-6-methyl-nicotinic acid methyl ester

Example 206

2-(4-Chloro-2-methoxy-6-methyl-phenoxy)-4-(1-ethyl-propylamino)-6-methyl-nicotinic acid methyl ester

30

1H NMR(CDCl₃) d 8.16-8.20 (m, 1H), 6.82 (d, 1H, J=1.5 Hz), 6.78 (d, 1H, J=1.5 Hz), 6.09 (s, 1H), 3.85 (s, 3H), 3.72 (s, 3H), 3.3-3.8 (m, 1H), 2.12 (s, 3H), 1.51-1.67 (m, 4H), 0.95 (t, 6H, J=7 Hz)ppm.

APCI+ m/z =407.2 (M+1), 409.2 (M+3)

Example 2082-(4-Chloro-2,6-dimethyl-phenoxy)-4-(1-methoxymethyl-propylamino)-6-methyl-nicotinic acid methyl ester

5 ^1H NMR(CDCl₃) d 8.2(d,1H), 7.02(s,2H), 6.14(s,1H), 3.87(s,3H), 3.6(m,1H),
 3.56(m,1H), 3.4(m,1H), 3.39(s,3H), 2.10(s,3H), 2.07(s,6H), 1.78(m,1H), 1.61(m,1H),
 1.00(t,3H)ppm.

Example 2092-(4-Bromo-2-methoxy-phenoxy)-4-(1-ethyl-propylamino)-6-methyl-nicotinic acid methyl ester

10 ^1H NMR(CDCl₃) d 8.14 (br d, 1H), 7.03-7.07 (m, 2H), 6.88 (d, 1H, J=8 Hz), 6.14 (s, 1H), 3.82 (s, 3H), 3.77 (s, 3H), 3.32-3.37 (m, 1H), 2.18 (s, 3H), 1.49-1.68 (m, 4H), 0.94 (t, 6H, J=7 Hz)
 APCI+ m/z = 437.1 (M+1), 439.1 (M+3)

Example 2102-(4-Chloro-2-hydroxy-phenoxy)-4-(1-ethyl-propylamino)-6-methyl-nicotinic acid methyl ester

The title compound was prepared by reacting 2-(4-chloro-2-methoxy-phenoxy)-4-(1-ethyl-propylamino)-6-methyl-nicotinic acid methyl ester with BBr₃ in methylene chloride at rt until all starting material was consumed. Standard work-up procedure gave the title
 20 compound.

APCI+ m/z = 379.2 (M+1), 381.2 (M+3)

Example 2112-(4-Chloro-2-ethoxy-phenoxy)-4-(1-ethyl-propylamino)-6-methyl-nicotinic acid methyl ester

25 ^1H NMR(CDCl₃) d 8.10 (br d, 1 H), 6.98 (d, 1H, J=8 Hz), 6.86-6.91 (m, 2H), 6.14 (s, 1H), 3.97 (q, 2H, J=7 Hz), 3.83 (s, 3H), 3.32-3.37 (m, 1H), 2.16 (s, 3H), 1.50-1.68 (m, 4H), 1.19 (t, 3H, J=7 Hz), 0.94 (t, 6H, J=7 Hz) ppm. APCI+ m/z = 407.1 (M+1), 409.1 (M+3)

Example 2124-(2-Hydroxy-1-hydroxymethyl-ethylamino)-2-(4-methoxy-2,6-dimethyl-phenoxy)-6-methyl-nicotinic acid methyl ester

30 ^1H NMR(CDCl₃) 8.42(d, 1H), 7.02(s, 2H), 6.17(s, 1H), 3.89(m, 2H), 3.86(s, 3H), 3.85(m, 2H), 3.67(m, 1H), 2.10(s, 3H), 2.05(s, 6H)ppm

Example 2134-(1-Carboxy-propylamino)-2-(4-chloro-2,6-dimethyl-phenoxy)-6-methyl- nicotinic acidmethyl ester

A mixture of 2-(4-chloro-2,6-dimethyl-phenoxy)-4-(1-formyl-propylamino)-6-methyl-nicotinic acid methyl ester, 2-methyl-2-butene, excess NaClO₂, and NaH₂PO₄ was stirred at rt for 15 min. The mixture was quenched with sat. sodium bicarbonate and extracted with hexane. The aqueous layer was acidified to pH 4 and extracted twice with diethyl ether. The organic layer was separated, dried and concentrated to give the title compound. The crude material was purified by silica gel column chromatography to give the desired product as a white crystal after recrystallization. Anal. For C₂₀H₂₃N₂O₅Cl calc., C, 59.04; H, 5.70; N, 6.89; found C, 59.29; H, 5.73; N, 6.83.

Example 2144-(1-Carboxy-propylamino)-2-(4-chloro-2,6-dimethyl-phenoxy)-5-chloro-6-methyl- nicotinic acid methyl ester

The title compound was prepared by the method analogous to that in Example 213, except with stirring overnight in the absence of 2-methyl-2-butene instead of a 15 minute reaction time.

Example 2154-(1-Carbamoyl-propylamino)-5-chloro-2-(4-chloro-2,6-dimethyl-phenoxy)-6-methyl-nicotinic acid methyl ester

A mixture of 4-(1-carboxy-propylamino)-2-(4-chloro-2,6-dimethyl-phenoxy)-5-chloro-6-methyl-nicotinic acid methyl ester with excess of thionyl chloride in methylene chloride and stirred for 15 min. The mixture was concentrated to dryness. The residue was diluted with methylene chloride and ammonium was bubbled into the reaction mixture. After stirring for 30 min, the mixture was quenched with water, extracted with methylene chloride. The organic layer was concentrated to dryness. The residue was purified by silica gel Biotage to give the title compound. ¹HNMR(CDCl₃) 7.02(s, 2H), 6.34(s, 1H), 5.92(d, 1H), 5.81(s, 1H), 4.05(m, 1H), 3.92(s, 3H), 2.27(s, 3H), 2.05(s, 6H), 1.80(m, 2H), 1.00(t, 3H)ppm

The following compounds (Examples 216-223) were prepared by a method similar to that described above starting with a carboxylic acid and excess of thionyl chloride in methylene, concentration, quenching with ammonium, alkylamine, dialkylamine or alkanol (eg., methanol, ethanol, etc.):

Example 2162-(4-Chloro-2,6-dimethyl-phenoxy)-4-(1-methoxycarbonyl-propylamino)-6-methyl-nicotinic acid methyl ester

5 1HNMR(CDCl₃) 8.52(d, 1H), 7.02(s, 2H), 5.97(s, 1H), 4.09(m, 1H), 3.89(s, 3H), 3.78(s, 3H), 2.09(s, 3H), 2.06(s, 6H), 1.98(m, 2H), 1.04(t, 3H) ppm

Example 2174-(1-Carbamoyl-propylamino)-2-(4-chloro-2,6-dimethyl-phenoxy)-6-methyl-nicotinic acid methyl ester

10 1H NMR(CDCl₃)d 8.56(d, 1H), 7.04(s, 2H), 6.38(s, 1H), 6.12(s, 1H), 5.44(s, 1H), 3.91(s, 3H), 3.88(m, 1H), 2.15(s, 1H), 2.07(s, 1H), 1.95(m, 2H), 1.24(t, 3H) ppm

Example 2182-(4-Chloro-2,6-dimethyl-phenoxy)-6-methyl-4-(1-methylcarbamoyl-propylamino)-nicotinic acid methyl ester

15 1HNMR(CDCl₃) 8.49(d, 1H), 7.05(s, 2H), 6.48(s, 1H), 6.08(s, 1H), 3.91(s, 3H), 3.90(m, 1H), 2.83(m, 3H), 2.15(s, 3H), 2.08(m, 6H), 1.08(t, 3H) ppm

Example 2195-Chloro-2-(4-chloro-2,6-dimethyl-phenoxy)-6-methyl-4-(1-methylcarbamoyl-propylamino)-nicotinic acid methyl ester

20 1HNMR(CDCl₃) 7.02(s, 2H), 6.42(m, 1H), 5.80(m, 1H), 3.96(m, 1H), 3.89(s, 3H), 2.86(d, 3H), 2.28(s, 3H), 2.04(m, 6H), 1.78(m, 2H), 0.98(t, 3H) ppm

Example 2202-(4-Chloro-2,6-dimethyl-phenoxy)-4-(1-dimethylcarbamoyl-propylamino)-6-methyl-nicotinic acid methyl ester

25 1HNMR(CDCl₃) 8.67(d, 1H), 7.02(s, 2H), 5.97(s, 1H), 4.39(m, 1H), 3.89(s, 3H), 3.13(s, 3H), 3.02(s, 3H), 2.13(s, 3H), 2.06(m, 6H), 1.92(m, 2H), 1.00(t, 3H) ppm

Example 2215-Chloro-2-(4-chloro-2,6-dimethyl-phenoxy)-4-(1-dimethylcarbamoyl-propylamino)-6-methyl-nicotinic acid methyl ester

30 1HNMR(CDCl₃) 7.02(s, 2H), 6.42(d, 1H), 4.66(m, 1H), 3.93(s, 3H), 3.06(s, 3H), 3.01(s, 3H), 2.27(s, 3H), 1.82(m, 2H), 0.90(t, 3H) ppm

Example 2222-(4-Chloro-2,6-dimethyl-phenoxy)-6-methyl-4-[1-(pyrrolidine-1-carbonyl)-propylamino]-nicotinic acid methyl ester

35 1HNMR(CDCl₃) 8.61(d, 1H), 7.02(s, 2H), 5.97(s, 1H), 4.20(m, 1H), 3.89(s, 3H), 3.59(m, 4H), 2.13(s, 3H), 2.01(m, 12H), 1.02(t, 3H) ppm

Example 2235-Chloro-2-(4-chloro-2,6-dimethyl-phenoxy)-6-methyl-4-[1-pyrrolidine-1-carbonyl]-propylamino]-nicotinic acid methyl ester

1H NMR(CDCl₃) 7.02(s, 2H), 6.41(d, 1H), 4.44(m, 1H), 3.93(s, 3H), 3.56(m, 2H),
 5 3.47(m, 2H), 2.26(s, 3H), 2.06(s, 6H), 2.00(m, 6H), 0.91(t, 3H)ppm

Example 2242-(4-Chloro-2,6-dimethyl-phenoxy)-6-methyl-4-(1-methylaminomethyl-propylamino)-nicotinic acid methyl ester

A mixture of 2-(4-chloro-2,6-dimethyl-phenoxy)-4-(1-formyl-propylamino)-6-methyl-nicotinic acid methyl ester (67 mg, 0.17 mmol) in dichloroethane (2 ml) was treated with methylamine, 1 drop of acetic acid, anhydrous Na₂SO₄ and sodium cyanoborohdride and stirred at rt. overnight. The mixture was quenched with water, extracted with methylene chloride. The organic layer was separated, dried, concentrated, and purified by silica gel Biotage using methylene chloride to 5% methanol in methylene chloride as eluent to give the title compound as an off-white solid. 1H NMR(CDCl₃) 8.07(d, 1H), 7.02(s, 2H), 6.29(s, 1H), 3.87(s, 3H), 3.80(m, 1H), 2.88(m, 2H), 2.56(s, 3H), 2.11(s, 3H), 2.06(s, 6H), 1.63(m, 2H), 0.99(t, 3H)ppm

The following compounds (Examples 225-227) were prepared in a similar reductive amination method as described in Example 224.

Example 2252-(4-Chloro-2,6-dimethyl-phenoxy)-6-methyl-4-(1-pyrrolidin-1-ylmethyl-propylamino)-nicotinic acid methyl ester

1H NMR(CDCl₃) 8.11(d, 1H), 6.99(s, 2H), 6.12(s, 1H), 3.84(s, 3H), 3.54(m, 1H), 3.43(m, 2H), 2.56(m, 4H), 2.07(s, 3H), 2.06(s, 6H), 1.84(m, 6H), .96(t, 3H)ppm

Example 2262-(4-Chloro-2,6-dimethyl-phenoxy)-4-(1-cyclopropylaminomethyl-propylamino)-6-methyl-nicotinic acid methyl ester

1H NMR(CDCl₃) d 8.07(d, 1H), 7.02(s, 2H), 6.31(s, 1H), 3.87(s, 3H), 3.79(m, 1H), 2.96(m, 1H), 2.36(m, 1H), 2.11(s, 3H), 2.07(s, 6H), 1.83(m, 1H), 1.61(m, 1H), 0.99(t, 3H), 30 0.98(m, 4H)ppm

Example 2272-(4-Chloro-2,6-dimethyl-phenoxy)-4-{1-[(cyclopropylmethyl-amino)-methyl]-propylamino}-6-methyl-nicotinic acid methyl ester

1H NMR(CDCl₃) d 8.07(d, 1H), 7.02(s, 2H), 6.55(s, 1H), 4.12(m, 1H), 3.88(s, 3H), 35 3.06(d, 2H), 2.87(m, 2H), 2.16(s, 3H), 2.05(s, 6H), 2.03(m, 1H), 1.69(m, 1H), 1.25(m, 1H), 1.03(t, 3H), 0.66(m, 2H), 0.38(m, 2H)ppm

Example 2282-(4-Chloro-2,6-dimethyl-phenoxy)-4-(1-ethylaminomethyl-propylamino)-6-methyl-nicotinic acid methyl ester

A solution of 2-(4-chloro-2,6-dimethyl-phenoxy)-4-(1-methanesulfonyloxyethyl-propylamino)-6-methyl-nicotinic acid methyl ester in acetonitrile was treated with sodium iodide, ethylamine and triethylamine. The resulting mixture was heated to 70°C overnight, then 85°C for 6 hrs, then 100°C overnight until tlc showed no starting material. The resulting mixture was quenched with water and extracted with ethyl acetate. The organic layer was separated, dried, concentrated, and purified to give the title compound as an oil. 1H NMR(CDCl₃) d 8.06(d, 1H), 7.02(s, 2H), 6.31(s, 1H), 3.88(s, 3H), 3.86(m, 1H), 2.85(m, 4H), 2.12(s, 3H), 2.07(s, 6H), 1.64(m, 1H), 1.60(m, 1H), 1.27(m, 3H), .99(t, 3H)

Example 2292-(4-Chloro-2,6-dimethyl-phenoxy)-4-{1-[(ethyl-methyl-amino)-methyl]-propylamino}-6-methyl-nicotinic acid methyl ester

1H NMR(CDCl₃) d 8.18 (d, 1H), 7.02(s, 2H), 6.19(m, 1H), 3.86(s, 3H), 3.56(m, 3H), 3.37(m, 2H), 2.11(s, 3H), 2.07(s, 6H), 1.80(m, 1H), 1.60(m, 2H), 1.25(m, 4H), 0.97(t, 3H) ppm

Example 2304-(1-Butylaminomethyl-propylamino)-2-(4-chloro-2,6-dimethyl-phenoxy)-6-methyl-nicotinic acid methyl ester

1H NMR(CDCl₃) d 8.07(d, 1H) 7.02(s, 1H), 6.25(s, 1H), 3.87(s, 3H), 3.79(m, 1H), 2.79(m, 2H), 2.69(m, 2H), 2.10(s, 3H), 2.07(s, 6H), 1.75(m, 2H), 1.57(m, 4H), 1.00(t, 3H), 0.92(t, 6H)ppm

Example 2312-(4-Chloro-2,6-dimethyl-phenoxy)-4-{1-[(cyclopropylmethyl-propyl-amino)-methyl]-propylamino}-6-methyl-nicotinic acid methyl ester

1H NMR(CDCl₃) d 8.01(d, 1H), 7.02(s, 2H), 6.13(s, 1H), 3.85(s, 3H), 3.48(m, 1H), 2.58(m, 2H), 2.37(m, 1H), 2.09(s, 3H), 2.07(s, 6H), 1.82(m, 1H), 1.42(m, 2H), 1.25(m, 4H), 0.97(t, t, 3H), 0.86(m, 6H) ppm

Example 2322-(4-Chloro-2,6-dimethyl-phenoxy)-6-methyl-4-(1-propylaminomethyl-propylamino)-nicotinic acid methyl ester

1H NMR(CDCl₃) d 8.09(d, 1H), 7.02(s, 2H), 6.19(s, 1H), 3.86(s, 3H), 3.60(m, 1H), 2.76(m, 2H), 2.61(t, 2H), 2.10(s, 3H), 2.07(s, 6H), 1.61(m, 6H), 0.97(t, 3H), 0.91(t, 3H)ppm

Example 2332-(4-Chloro-2,6-dimethyl-phenoxy)-4-(1-[(furan-2-ylmethyl)-amino]-methyl)-propylamino}-6-methyl-nicotinic acid methyl ester

5 1H NMR(CDCl₃) d 8.09(d, 1H), 7.37(s, 1H), 7.02(s, 2H), 6.31(dd, 2H), 6.17(s, 1H),
 3.87(s, 3H), 3.84(s, 2H), 3.58(m, 1H), 2.75(m, 2H), 2.09(s, 3H), 2.07(s, 6H), 1.70(m, 1H),
 1.58(m, 1H), 0.95(t, 3H)ppm

Example 2342-(4-Chloro-2,6-dimethyl-phenoxy)-4-{1-[(2-methoxy-ethyl)amino]-methyl}-propylamino}-6-methyl-nicotinic acid methyl ester

10 1H NMR(CDCl₃) d 8.10(d, 1H), 7.02(s, 2H), 6.19(s, 1H), 3.87(s, 3H), 3.61(m, 1H),
 3.51(m, 2H), 3.34(s, 3H), 2.84(m, 2H), 2.79(m, 2H), 2.10(s, 3H), 2.07(s, 6H), 1.71(m, 1H),
 1.57(m, 1H), 0.98(t, 3H)ppm

Example 2352-(4-Chloro-2,6-dimethyl-phenoxy)-4-(dimethylaminomethyl-propylamino)-6-methyl-nicotinic acid methyl ester

15 1HNMR(CDCl₃) 8.14(d, 1H), 7.02(s, 2H), 6.10(s, 1H), 3.86(s, 3H), 3.53(m, 1H),
 2.44(m, 2H), 2.29(s, 6H), 2.10(s, 3H), 2.07(s, 6H), 1.78(m, 1H), 1.56(m, 1H), 0.97(t, 3H)ppm

Example 2364-[(2-Butylamino-ethyl)-ethyl-amino]-2-(4-chloro-2,6-dimethyl-phenoxy)-6-methyl-nicotinic acid methyl ester

20 1HNMR(CDCl₃) 7.00(s, 2H), 6.31(s, 1H), 3.88(s, 3H), 3.41(t, 2H), 3.26(m, 2H), 2.82(t, 2H),
 2.65(t, 2H), 2.15(s, 3H), 2.05(s, 6H), 1.51(m, 2H), 1.34(m, 2H), 1.12(t, 3H), 0.89(t, 3H)ppm

Example 2372-(4-Chloro-2,6-dimethyl-phenoxy)-4-(S,S)-(1-ethyl-2-methylamino-propylamino)-6-methyl-nicotinic acid methyl ester

The title compound was prepared by a reductive amination as shown above starting with 2-(4-Chloro-2,6-dimethyl-phenoxy)-4-(1-ethyl-2-oxo-propylamino)-6-methyl-nicotinic acid methyl ester and methyl amine. APCI M+1 [420.2], 1H NMR(CDCl₃)

Example 2382-(4-Chloro-2,6-dimethyl-phenoxy)-4-(S,R)-(1-ethyl-2-methylamino-propylamino)-6-methyl-nicotinic acid methyl ester

The title compound was prepared by a reductive amination as shown above starting with 2-(4-Chloro-2,6-dimethyl-phenoxy)-4-(1-ethyl-2-oxo-propylamino)-6-methyl-nicotinic acid methyl ester and methyl amine. APCI M+1 [420.2], 1H NMR(CDCl₃)

Example 2392-(4-Methoxy-2,6-dimethyl-phenoxy)-6-methyl-4-(1-methylsulfanylmethyl-propylamino)-nicotinic acid methyl ester

A mixture of 2-(4-methoxy-2,6-dimethyl-phenoxy)-4-(1-methanesulfonyloxymethyl-propylamino)-6-methyl-nicotinic acid methyl ester and sodium iodide in acetonitrile was stirred at rt for 2 hr, then NaSMe was added. The mixture was heated at 60°C overnight. DMSO and additional NaSMe were added and heated for additional hours until all starting material was consumed. The mixture was quenched with water, extracted with ethyl acetate. The organic layer was separated, dried, concentrated, and purified to give the title compound.

10 $^1\text{H}\text{NMR}(\text{CDCl}_3)$ 8.23(d, 1H), 6.59(s, 2H), 6.10(s, 1H), 3.87(s, 3H), 3.78(s, 3H), 3.60(m, 1H), 2.75(m, 1H), 2.65(m, 1H), 2.14(s, 3H), 2.08(m, 9H), 1.85(m, 1H), 1.66(m, 1H), 1.00(t, 3H)ppm

The following compounds (Examples 240-243) were prepared by the method similar to that described in Example 239 starting with an appropriate 2-(substituted-phenoxy)-4-(1-methanesulfonyloxymethyl-propylamino)-3,6-substituted-pyridine with an appropriate nucleophile:

Example 2402-(4-Methoxy-2,6-dimethyl-phenoxy)-6-methyl-4-(1-[1,2,4]triazol-1-ylmethyl-propylamino)-nicotinic acid methyl ester

20 $^1\text{H}(\text{CDCl}_3)$ 8.23(d, 1H), 8.02(s, 1H), 7.95(s, 2H), 5.92(s, 1H), 6.59(s, 2H), 5.93(s, 1H), 4.31(m, 1H), 4.22(m, 1H), 3.93(m, 1H), 3.87(s, 3H), 3.77(s, 3H), 2.10(s, 3H), 2.07(s, 6H), 1.70(m, 1H), 1.59(m, 1H), 1.04(t, 3H)ppm

Example 2412-(4-Chloro-2,6-dimethyl-phenoxy)-6-methyl-4-(1-methylsulfanylmethyl-propylamino)-nicotinic acid methyl ester

25 $^1\text{H}\text{NMR}(\text{CDCl}_3)$ 8.27(d, 1H), 7.02(s, 2H), 6.12(s, 1H), 3.87(s, 3H), 3.61(m, 1H), 2.70(m, 2H), 2.17(s, 3H), 2.14(s, 3H), 2.08(s, 6H), 1.85(m, 2H), 1.00(t, 3H)ppm

Example 2422-(4-Chloro-2,6-dimethyl-phenoxy)-4-(2-ethyl-aziridin-1-yl)-6-methyl-nicotinic acidmethyl ester

30 7.02(s,2H), 6.38(s,1H), 3.95(s,3H), 2.27(m,1H), 2.18(s,3H), 2.15(m,2H), 2.06(s,6H), 1.75(m,1H), 1.63(m,1H), 1.06(t,3H)ppm.

Example 2432-(4-Chloro-2,6-dimethyl-phenoxy)-6-methyl-4-[1-(3H-[1,2,3]triazol-4-ylsulfanyl)methyl]-propylamino]-nicotinic acid methyl ester

5 $^1\text{H}\text{NMR}(\text{CDCl}_3)$ 8.32(d, 1H), 7.54(s, 1H), 6.95(s, 2H), 6.13(s, 1H), 3.87(s, 3H),
3.67(m, 1H), 3.20(m, 1H), 3.05(m, 1H), 2.05(m, 9H), 1.99(m, 1H), 1.67(m, 1H), 1.01(t,
3H)ppm

Example 2442-(4-Chloro-2,6-dimethyl-phenoxy)-4-(1-hydroxymethyl-3-methanesulfonyl)-propylamino)-6-methyl-nicotinic acid methyl ester

10 The title compound was prepared by oxidation of 2-(4-Chloro-2,6-dimethyl-phenoxy)-4-(1-hydroxymethyl-3-methylsulfanyl-propylamino)-6-methyl-nicotinic acid methyl ester with m-chloroperbenzoic acid in methylene chloride at rt. for 2 hrs. $^1\text{H}\text{NMR}(\text{CDCl}_3)$ d 8.32(d,1H), 7.04(s,2H), 6.23(s,1H), 3.88(s,3H), 3.7-3.9(m,3H), 3.1-3.3(m,2H), 2.95(s,3H), 2.0-2.4(m,2H), 2.13(s,3H), 2.07(s,6H) ppm.

15 The following compounds (Examples 245-248) were prepared by the method analogous to that described in Example 188:

Example 2452-(4-Ethoxy-2,6-dimethyl-phenoxy)-6-methyl-4-(tetrahydro-furan-3-ylamino)-nicotinic acid methyl ester

20 $^1\text{H}\text{NMR}(\text{CDCl}_3)$ d 8.35(d, 1H), 6.59(s, 2H), 6.08(s, 1H), 4.03(m, 1H), 4.01(m, 4H),
3.99(m, 1H), 3.92(s, 3H), 3.89(m, 1H), 2.34(m, 1H), 2.25(m, 3H), 2.08(s, 6H), 1.39(t, 3H)ppm

Example 2462-[4-(2-Methoxy-ethoxy)-2,6-dimethyl-phenoxy]-6-methyl-4-(tetrahydro-furan-3-ylamino)-nicotinic acid methyl ester

25 $^1\text{H}\text{NMR}(\text{CDCl}_3)$ d 8.30(d, 1H), 6.62(s, 2H), 6.07(s, 1H), 4.10(m, 3H), 4.02(m, 2H),
3.98(m, 1H), 3.85(s, 2H), 3.75(m, 3H), 3.45(s, 3H), 2.32(m, 1H), 2.19(s, 3H), 2.07(s, 6H)ppm

Example 2472-(2,6-Dimethyl-4-trifluoromethoxy-phenoxy)-6-methyl-4-(tetrahydro-furan-3-ylamino)-nicotinic acid methyl ester

30 $^1\text{H}\text{NMR}(\text{CDCl}_3)$ d 8.29 (d, 1H, J=6 Hz), 6.91 (s, 2H), 6.06 (s, 1H), 4.11-4.33 (m, 1H),
3.97-4.05 (m, 2H), 3.89-3.93 (m, 1H), 3.87 (s, 3H), 3.72-3.76 (m, 1H), 2.31-2.35 (m, 1H), 2.14
(s, 3H), 2.10 (s, 6H), 1.94-1.96 (m, 1H)ppm.

APCI+ m/z =441.2 (M+1)

Example 2482-(4-Chloro-2,6-dimethyl-phenoxy)-6-methyl-4-(R)-(tetrahydro-furan-3-ylamino)-nicotinic acid methyl ester

APCI+ m/z =391.3 (M+1)

Example 249

2-(4-Chloro-2,6-dimethyl-phenoxy)-4-(1-hydroxymethyl-3-iodo-propylamino)-6-methyl-nicotinic acid methyl ester

APCI [M+1] 518.9, 520.9

5

Example 250

2-(4-Chloro-2,6-dimethyl-phenoxy)-4-(1-hydroxymethyl-3-methanesulfinyl-propylamino)-6-methyl-nicotinic acid methyl ester

1H NMR(CDCl₃) d 8.31(d, 1H), 7.03(s, 2H), 6.24(s, 0.5H), 6.28(s, 0.5H), 3.87(s, 3H), 3.65-3.9(m, 3H), 2.7-3.0(m, 2H), 2.60(s, 3H), 2.0-2.4(m, 2H), 2.14(s, 3H), 2.07(s, 6H) ppm.

10

Example 251

2-(4-Cyclopropyloxy-2,6-dimethyl-phenoxy)-6-methyl-4-(tetrahydro-furan-3-ylamino)-nicotinic acid methyl ester

1H NMR (CDCl₃) d 8.32(d, 1H), 6.73(s, 2H), 6.07(s, 1H), 4.13(m, 1H), 4.01(m, 4H), 3.98(m, 1H), 3.85(s, 3H), 3.72(m, 2H), 2.22(s, 3H), 2.09(s, 6H), .87(m, 2H), .75(m, 4H)ppm

15

Example 252

2-(4-Chloro-2,6-dimethoxy-phenoxy)-6-methyl-4-(tetrahydro-furan-3-ylamino)-nicotinic acid methyl ester

Example 253

20 4-sec-Butylamino-6-methyl-2-(2,4,6-trimethyl-pyridin-3-yloxy)-nicotinic acid methyl ester

1H NMR(CDCl₃) 8.08(d, 1H), 6.86(s, 1H), 6.09(s, 1H), 3.86(s, 3H), 3.48(m, 1H), 2.49(s, 3H), 2.31(s, 3H), 2.08(s, 6H), 1.63(m, 2H), 1.21(d, 3H), 0.98(t, 3H)ppm

Example 254

25 2-(4-Chloro-2,6-dimethyl-phenoxy)-4-[ethyl-[2-(ethyl-methyl-amino)-ethyl]-amino]-6-methyl-nicotinic acid methyl ester

Example 255

2-(4-Chloro-2,6-dimethyl-phenoxy)-4-[ethyl-(2-propylamino-ethyl)-amino]-6-methyl-nicotinic acid methyl ester

Example 256

30 4-(1-Ethyl-propylamino)-6-methyl-2-(2,4,6-trimethyl-pyridin-3-yloxy)-nicotinic acid methyl ester

1H NMR(CDCl₃) 8.09(d, 1H), 6.86(s, 1H), 6.08(s, 1H), 3.86(s, 3H), 3.33(m, 1H), 2.49(s, 3H), 2.31(s, 3H), 2.07(s, 6H), 1.63(m, 4H), 0.94(t, 6H)ppm

1H NMR(CDCl₃) d 8.39 d, 1H, J= 6Hz, 6.63 (s, 2H), 6.06 (s, 1H), 4.08-4.15 (m, 1H),

35 3.95-4.05 (m, 2H), 3.88-3.92 (m, 1H), 3.86 (s, 3H), 3.73 (s, 6H), 3.67-3.73 (m, 1H), 2.26-2.35 (m, 1H), 2.14 (s, 3H), 1.89-1.96 (m, 1H) ppm.

The following Examples 257-287 relate to other compounds of formula I of the invention, wherein R₄ is -C(O)NR₂₄R₂₅:

The following compounds (Examples 257-280) were prepared by a method analogous to that in Example 113 starting with the corresponding nicotinic acid or pyrimidine-5-carboxylic derivative and quenching with an appropriate nucleophile; these compounds can also be prepared by coupling of 2-(substituted-phenoxy)-6-methyl-4-chloro-nicotinamide and/or -N-substituted-nicotinamide with an appropriate amine in NMP at 130-160°C:

Example 257

10 2-(4-Chloro-2,6-dimethyl-phenoxy)-6-methyl-4-(tetrahydro-furan-3-ylamino)-nicotinamide

1H NMR(CDCl₃) d 9.99(d,1H), 7.85(brs, 1H), 7.07(s,2H), 6.13(s,1H), 5.62(brs,1H), 3.7-4.2(m,5H), 2.95(d,3H), 2.31(m,1H), 2.20(s,3H), 2.09(s,6H), 2.01(m,1H) ppm.

Example 258

15 2-(4-Chloro-2,6-dimethyl-phenoxy)-4-(1-hydroxymethyl-3-methylsulfanyl-propylamino)-6-methyl-nicotinamide

1H NMR(CDCl₃) d 9.78(d,1H), 7.97(brs, 1H), 7.06(s,2H), 6.32(s,1H), 5.77(brs,1H), 3.6-3.9(m,3H), 2.5-2.7(m,2H), 2.0-2.2(m,12H), 1.8-2.0(m,2H)ppm.

Example 259

20 2-(4-Chloro-2,6-dimethyl-phenoxy)-6,N-dimethyl-4-(S)-(tetrahydro-furan-3-ylamino)-nicotinamide

1H NMR(CDCl₃) d 10.00(d,1H), 8.05(brs, 1H), 7.06(s,2H), 6.10(s,1H), 4.09(m,1H), 3.96-4.05(m,3H), 3.73(m,1H), 2.95(d,3H), 2.31(m,1H), 2.12(s,3H), 2.06(s,6H), 1.96(m,1H) ppm.

Example 260

25 2-(4-Chloro-2,6-dimethyl-phenoxy)-4-(1-ethyl-propylamino)-6,N-dimethyl-nicotinamide

1H NMR(CDCl₃) d 9.78(d,1H), 8.10(brs, 1H), 7.06(s,2H), 6.13(s,1H), 3.32(m,1H), 2.96(d,3H), 2.09(s,3H), 2.08(s,6H), 1.65(m,4H), 0.96(t,6H)ppm.

Example 261

30 4-sec-Butylamino-2-(4-chloro-2,6-dimethyl-phenoxy)-6,N-dimethyl-nicotinamide

1H NMR(CDCl₃) d 9.78(d,1H), 8.04(brs, 1H), 7.07(s,2H), 6.14(s,1H), 3.46(m,1H), 2.95(d,3H), 2.15(s,3H), 2.09(s,6H), 1.158(m,2H), 1.23(d,3H), 0.99(t,6H)ppm.

Example 262

4-(1-Ethyl-propylamino)-2-(4-methoxy-2,6-dimethyl-phenoxy)-6-methyl-nicotinamide

Mp=184°C Found: C, 67.68, H, 8.12, N, 10.81; Calcd: C, 67.90, H, 7.87, N, 11.31 .

35 1H(CDCl₃) 9.67(d, 1H), 8.06(m, 1H) 6.61(s, 2H), 6.11(s, 1H), 5.48(s, 1H), 3.79(s, 3H), 3.32(m, 1H), 2.09(s, 9H), 1.61(s, 4H), 0.95(t, 6H)ppm

Example 263

4-(1-Ethyl-propylamino)-2-(4-methoxy-2,6-dimethyl-phenoxy)-6,N-dimethyl-nicotinamide

1H(CDCl₃) 9.78(d, 1H), 8.22(m, 1H), 6.60(s, 2H), 6.10(s, 1H), 3.78(s, 3H), 3.25(m, 1H), 2.93(d, 3H), 2.07(s, 9H), 1.61(m, 4H), 0.95(t, 6H)ppm

Example 264

2-(4-Methoxy-2,6-dimethyl-phenoxy)-4-(1-methoxymethyl-propylamino)-6-methyl-nicotinamide

1HNMR(CDCl₃) 9.80(d, 1H), 8.04(s, 1H), 6.61(s, 2H), 6.18(s, 1H), 5.62(s, 1H), 3.78(s, 3H), 3.51(m, 2H), 3.39(s, 3H), 2.09(s, 3H), 2.08(s, 6H), 1.79(m, 1H), 1.59(m, 1H), 0.99(t, 3H)ppm

Example 265

2-(4-Methoxy-2,6-dimethyl-phenoxy)-4-(1-methoxymethyl-propylamino)-6,N-dimethyl-nicotinamide

1HNMR(CDCl₃) 9.92(d, 1H), 8.22(s, 1H), 6.62(s, 2H), 6.19(s, 1H), 3.79(s, 3H), 3.5(m, 2H), 3.38(s, 3H), 2.94(d, 3H), 2.12(s, 3H), 2.08(s, 6H), 1.80(m, 1H), 1.61(m, 1H), 1.00(t, 3H)ppm

Example 266

4-(1-Hydroxymethyl-propylamino)-2-(4-methoxy-2,6-dimethyl-phenoxy)-6,N-dimethyl-nicotinamide

1HNMR(CDCl₃) 9.79(d, 1H), 8.28(d, 1H), 6.62(s, 2H), 6.24(s, 1H), 3.79(s, 3H), 3.70(m, 2H), 3.54(m, 1H), 2.94(d, 3H), 2.08(s, 6H), 1.62(m, 2H), 1.01(t, 3H)ppm

Example 267

4-sec-Butylamino-2-(4-methoxy-2,6-dimethyl-phenoxy)-6,N-dimethyl-nicotinamide

1HNMR(CDCl₃) 9.76(d, 1H), 8.26(d, 1H), 6.61(s, 2H), 6.12(s, 1H), 3.79(s, 3H), 3.46(m, 1H), 2.94(d, 3H), 2.09(s, 3H), 2.07(s, 6H), 1.64(m, 2H), 1.24(m, 3H), 0.98(t, 3H)ppm

Example 268

2-(4-Chloro-2,6-dimethyl-phenoxy)-4-(S)-(1-methoxymethyl-propylamino)-6,N-dimethyl-nicotinamide

Anal. For C₂₁H₂₈ClN₃O₃ calc. C, 62.14% H, 6.95%, N, 10.35%; found C, 62.12%, H, 6.95%, N, 10.42%.

Example 269

2-(4-Chloro-2,6-dimethyl-phenoxy)-4-(S)-(1-methoxymethyl-propylamino)-6-methyl-nicotinamide

Anal. For C₂₀H₂₆ClN₃O₃ calc. C, 61.30% H, 6.69%, N, 10.725%; found C, 60.97%, H, 6.53%, N, 10.47%.

Example 2702-(4-Chloro-2,6-dimethyl-phenoxy)-6,N-dimethyl-4-(1-methylsulfanylmethyl-propylamino)-nicotinamide

5 1HNMR(CDCl₃) 9.97(d, 1H), 8.1(brs, 1H), 7.06(s, 2H), 6.16(s, 1H), 3.56(m, 1H),
 2.96(s, 3H), 2.6-2.8(m, 2H), 2.17(s, 3H), 2.11(s, 3H), 2.08(s, 6H), 1.6-1.9(m, 2H), 1.24(m, 3H),
 1.00(t, 3H)ppm

Example 2712-(4-Chloro-2,6-dimethyl-phenoxy)-6-methyl-4-(1-methylsulfanylmethyl-propylamino)-nicotinamide

10 1HNMR(CDCl₃) 9.89(d, 1H), 7.9(brs, 1H), 7.06(s, 2H), 6.16(s, 1H), 3.56(m, 1H), 2.6-
 2.8(m, 2H), 2.17(s, 3H), 2.11(s, 3H), 2.07(s, 6H), 1.6-1.9(m, 2H), 1.24(m, 3H), 0.99(t, 3H)ppm

Example 2722-(4-Chloro-2-methoxy-phenoxy)-4-(1-ethyl-propylamino)-6,N-dimethyl-nicotinamide

15 1H NMR(CDCl₃) d 9.40 (d, 1H, J=8 Hz), 8.10 (br s, 1H), 7.17 (d, 1H, J=9 Hz), 6.94-
 6.96 (m, 2H), 6.14 (s, 1H), 3.79 (s, 3H), 3.27-3.31 (m, 1H), 2.93 (d, J=5 Hz) 2.14 (s, 3H),
 1.51-1.66 (m, 4H), 0.95 (t, 6H, J=7 Hz) ppm.. Cl+ m/z =392.2 (M+1), 394.2 (M+3)

Example 2732-(4-Chloro-2-methoxy-phenoxy)-4-(1-ethyl-propylamino)-6-methyl-nicotinamide

20 1H NMR(CDCl₃) d 9.40 (d, 1H), 7.92 (brs, 1H), 7.17 (d, 1H, J=9 Hz), 6.94-6.96 (m,
 2H), 6.15 (s, 1H), 5.48 (br s, 1H), 3.77 (s, 3H), 3.28-3.36 (m, 1H), 2.16 (s, 3H), 1.52-1.66 (m,
 4H), 0.94 (t, 6H, J=7 Hz) ppm.
 APCI+ m/z =378.1 (M+1), 380.1 (M+3)

Example 2742-(4-Chloro-2,6-dimethyl-phenoxy)-4-(1-cyclopropylmethoxymethyl-propylamino)-6-

25 methyl-nicotinamide

1H NMR(CDCl₃) d 9.70 (d, 1H), 7.90 (brs, 1H), 7.05 (s, 1H), 6.22 (s, 1H), 5.6 (br s,
 1H), 3.57 (m, 2H), 3.43(m,1H), 3.33(d,3H), 2.09(s,6H), 2.07 (s, 3H), 1.5-1.9 (m, 2H), 0.9-
 1.0(m,4H), 0.53(m,2H), 0.50(m,2H) ppm.

Example 2752-(4-Chloro-2,6-dimethyl-phenoxy)-4-(1-ethoxymethyl-propylamino)-6-methyl-nicotinamide

30 1H NMR(CDCl₃) d 9.75 (d, 1H), 7.90 (brs, 1H), 7.05 (s, 1H), 6.21 (s, 1H), 5.6 (br s,
 1H), 3.3-3.6(m,4H), 2.08(s,6H), 2.07 (s, 3H), 1.5-1.9 (m, 2H), 1.20(t,3H), 1.00(t,3H) ppm.

Example 276

2-(4-Chloro-2,6-dimethyl-phenoxy)-4-(1-ethoxymethyl-propylamino)-N-ethyl-6-methyl-nicotinamide

5 1H NMR(CDCl₃) d 9.78 (d, 1H), 8.09 (t, 1H), 7.06 (s, 1H), 6.22 (s, 1H), 5.6 (br s, 1H),
3.3-3.6(m,6H), 2.09(s,3H), 2.08 (s, 6H), 1.5-1.9 (m, 2H), 1.20-1.4(m,6H), 1.00(t,3H) ppm.

Example 277

2-(4-Chloro-2,6-dimethyl-phenoxy)-4-(1-ethoxymethyl-propylamino)-6,N-dimethyl-nicotinamide

10 1H NMR(CDCl₃) d 9.8(d, 1H), 8.1 (brs, 1H), 7.06 (s, 1H), 6.22 (s, 1H), 3.54(m,3H),
3.38(m,1H), 2.94(d,3H), 2.08(s,6H), 2.07 (s, 3H), 1.83(m,1H), 1.60(m,1H), 1.20(t,3H),
1.00(t,3H) ppm.

Example 278

2-(4-Bromo-2-methoxy-phenoxy)-4-(1-ethyl-propylamino)-6,N-dimethyl-nicotinamide

15 1H NMR(CDCl₃) d 9.41 (br d, 1H), 8.08 (br s, 1H), 7.09-7.12 (m, 3H), 6.15 (s, 1H),
3.79 (s, 1H), 3.28-3.33 (m, 1H), 2.93 (d, 3H, J=5 Hz), 2.15 (s, 3H), 1.501-1.65 (m, 4H), 0.95
(t, 6H, J=8 Hz)
APCI+ m/z = 436.1 (M+1), 438.1 (M+3)

Example 279

2-(4-Bromo-2-methoxy-phenoxy)-4-(1-ethyl-propylamino)-6-methyl-nicotinamide

20 1H NMR(CDCl₃) d 9.39 (br d, 1H), 7.91 (br s, 1H), 7.09-7.11 (m, 3H), 6.15 (s, 1H),
5.49 (br s, 1H), 3.77 (s, 3H), 3.29-3.34 (m, 1H), 2.15 (s, 3H), 1.51-1.67 (m, 4H), 0.94 (t, 6H,
J=7Hz) ppm.

APCI+ m/z = 422.1 (M+1), 424.1 (M+3)

Example 280

2-(4-Chloro-2,6-dimethyl-phenoxy)-4-(1-chloromethyl-propylamino)-6-methyl-nicotinamide

25 1H NMR(CDCl₃) d 9.93(d,1H), 7.9(brs,1H), 7.06(s,2H), 6.16(s,1H), 5.6(brs,1H), 3.4-
3.7(m,3H), 2.1(s,3H), 2.08(s,6H), 1.9(m,1H), 1.65(m,1H), 1.03(t,3H) ppm.

Example 281

2-(4-Chloro-2,6-dimethyl-phenoxy)-4-(1-formyl-propylamino)-6-methyl-nicotinamide

30 A mixture of 2-(4-chloro-2,6-dimethyl-phenoxy)-4-(1-hydroxymethyl-propylamino)-6-
methyl-nicotinamide and Dess-Martin reagent in methylene chloride/DMSO was stirred at rt
for 4 hr. The title compound was isolated after standard work-up and silica gel Biotage
purification. 1H NMR(CDCl₃) d 9.52(s,1H), 8.00(brs,1H), 7.06(s,22H), 5.99(s,1H), 5.8(brs,1H),
3.85(m,1H), 2.09(s,3H), 2.08(s,6H), 1.8-2.2(m,2H), 1.08(t,3H) ppm.
35

Example 2824-(1-Formyl-propylamino)-2-(4-methoxy-2,6-dimethyl-phenoxy)-6,N-dimethyl-nicotinamide

The title compound was prepared by a method analogous to that described in
5 Example 281.

1HNMR(CDCl₃) 9.51(s, 1H), 8.32(m, 1H), 6.62(s, 2H), 5.97(s, 1H), 3.81(m, 1H),
3.79(s, 3H), 2.96(m, 3H), 2.08(m, 9H), 1.89(m, 2H), 1.09(t, 3H)ppm

Example 2832-(4-Chloro-2,6-dimethyl-phenoxy)-4-(1-ethyl-2-hydroxy-propylamino)-6-methyl-nicotinamide

To a solution of MeMgBr in dry THF was added a solution of 2-(4-chloro-2,6-dimethyl-phenoxy)-4-(1-formyl-propylamino)-6-methyl-nicotinamide in dry THF at -78°C. The mixture was stirred at -78°C for 2 hr, then quenched with dilute acid. After standard extraction and purification, the title compound was obtained. 1H NMR(CDCl₃) d 9.8(d,1H), 7.9(nbrs,1H),
15 7.05(s,2H), 6.27(s,0.5H), 6.24(s,0.5H), 5.6(brs,1H), 3.91(m,0.5H), 3.89(m,0.5H),
3.51(m,0.5H), 3.3(m,0.5H), 2.09(s,9H), 1.5-1.8(m,2H), 1.26(d,3H), 0.98(t,3H) ppm.

Example 2844-(1-Ethyl-2-methoxy-propylamino)-2-(4-methoxy-2,6-dimethyl-phenoxy)-6,N-dimethyl-nicotinamide

20 1HNMR(CDCl₃) 9.87(d, 1H), 8.26(d, 1H), 6.61(s, 2H), 6.16(s, 1H), 3.79(s, 3H),
3.46(m, 1H), 3.40(s, 3H), 2.94(d, 3H), 2.08(s, 9H), 1.76(m, 1H), 1.65(m, 1H), 1.25(m, 1H),
1.17(d, 3H), 0.98(t, 3H)ppm mp = 122.6°C

Example 2852-(4-Bromo-2,6-dimethyl-phenoxy)-4-(1-ethyl-propylamino)-6-methyl-nicotinamide

25 To a mixture of 2-chloro-4-(1-ethyl-propylamino)-6-methyl-nicotinamide and 2,6-dimethyl-4-bromo-phenol in NMP was added t-BuOK. The resulting mixture was heated in a 160°C oil bath overnight. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was separated, dried and concentrated, then purified through silica gel Biotage to give the title compound. 1H NMR(CDCl₃) d 9.69(d,1H), 7.89(brs,1H),
30 7.20(s,2H), 6.13(s,1H), 5.5(brs,1H), 3.3(m,1H), 2.10(s,3H), 2.09(s,6H), 1.6(m,4H), 0.95(t,6H)
ppm.

Example 2864-(1-Ethyl-propylamino)-6,N-dimethyl-2-(2,4,6-trimethyl-pyridin-3-yloxy)-nicotinamide

1H(CDCl₃) 9.74(d, 1H), 8.08(s, 1H), 6.90(s, 1H), 6.12(s, 1H), 3.31(m,1H), 2.96(d, 3H),
35 2.51(s, 3H), 2.30(s, 3H), 2.08(s, 3H), 2.05(s, 3H), 1.60(m, 4H), 0.95(t, 3H)ppm

Example 2874-(1-Ethyl-propylamino)-6-methyl-2-(2,4,6-trimethyl-pyridin-3-yloxy)-nicotinamide

MP=164.3°C 1H NMR (CDCl₃) 9.65(d, 1H), 7.8(s, 1H), 6.91(s, 1H), 6.14(s, 1H),
 5.50(s, 1H), 3.32(m, 1H), 2.53(s, 3H), 2.34(s, 3H), 2.17(s, 3H), 2.10(s, 3H), 1.60(m, 4H),
 5 0.95(t, 6H)ppm

The following Examples 288-294 relate to other compounds of formula I of the invention, wherein R₄ is -C(O)R₂₄, for example -C(O)CH₃:

Example 288

1-[4-(1-Ethyl-propylamino)-2-(4-methoxy-2,6-dimethyl-phenoxy)-6-methyl-pyridin-3-yl]-ethanone
 10 1H NMR(CDCl₃) 9.74(d, 1H), 6.61(s, 2H), 6.10(s, 1H), 3.79(s, 3H), 3.39(m, 1H),
 2.73(s, 3H), 2.10(s, 9H), 1.62(m, 4H), 0.94(t, 6H)ppm

Example 289

N-[3,6-Dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-N-(2-pyrrolidin-1-yl-ethyl)-acetamide
 15 1H NMR(CDCl₃) d 6.89 (s, 2H), 6.60 (s, 1H), 4.00-4.07 (m, 1H), 3.53-3.59 (m, 1H),
 2.59-2.72 (m, 2H), 2.52 (br s, 4H), 2.30 (s, 3H), 2.24 (s, 3H), 2.22 (s, 3H), 2.04 (s, 6H), 1.84
 (s, 3H), 1.74 (br s, 4H) ppm.

Example 290

N-[3,6-Dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-N-(2-pyrrolidin-1-yl-ethyl)-isobutyramide
 20 1H NMR(CDCl₃) d 6.89 (s, 2H), 6.56 (s, 1H), 4.09-4.17 (m, 1H), 3.38-3.48 (m, 1H),
 2.65-2.77 (m, 2H), 2.61 (br s, 4H), 2.33-2.40 (m, 1H), 2.30 (s, 3H), 2.24 (s, 3H), 2.20 (s, 3H),
 2.05 (s, 6H), 1.77 (br s, 4H), 1.04 (t, 6H, J = 7 Hz) ppm.

Example 291

N-[3,6-Dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-N-(2-pyrrolidin-1-yl-ethyl)-malonamic acid ethyl ester
 25 1H NMR(CDCl₃) d 6.89 (s, 2H), 6.63 (s, 1H), 4.11-4.17 (m, 3H), 3.44-3.56 (m, 1H),
 3.15 (s, 2H), 2.72 (br s, 2H), 2.57 (br s, 4H), 2.30 (s, 3H), 2.24 (s, 3H), 2.23 (s, 3H), 2.04 (s,
 30 6H), 1.77 (br s, 4H), 1.24 (t, 3H, J=7 Hz)

Example 292

2-(4-Chloro-2,6-dimethyl-phenoxy)-4-cyclopentylamino-6-methyl-pyridine-3-carbaldehyde
 35 1H NMR(CDCl₃) d 9.42(d,1H), 7.05(s,2H), 6.09(s,1H), 4.18(brs,1H), 4.06(m,2H),
 3.95(m,1H), 3.77(m,1H), 2.35(m,1H), 2.17(s,3H), 2.09(s,6H), 1.98(m,1H) ppm.

Example 2934-(1-Ethyl-propylamino)-2-(4-methoxy-2,6-dimethyl-phenoxy)-6-methyl-pyridine-3-carbaldehyde

5 1HNMR(CDCl₃) 9.26(d, 1H), 6.60(s, 2H), 6.10(s, 1H), 3.78(s, 3H), 3.40(m, 1H),
 2.14(s, 3H), 2.11(s, 6H), 1.66(m, 4H), 0.96(t, 6H)ppm

Example 294

10 1-[2-(4-Chloro-2-methoxy-phenoxy)-4-(1-ethyl-propylamino)-6-methyl-pyridin-3-yl]-ethanone
 1H NMR(CDCl₃) d 9.59 (br d, 1H), 6.93-7.02 (m, 3H), 6.14 (s, 1H), 3.78 (s, 3H), 3.33-
 3.38 (m, 1H), 2.69 (s, 3H), 2.14 (s, 3H), 1.49-1.67 (m, 4H), 0.94 (t, 6H, J=7 Hz) ppm.

The following Examples 295-329 relate to other compounds of formula I of the invention, wherein R₄ is methyl:

Example 295

15 sec-Butyl-[2-(2,6-dimethyl-4-trifluoromethoxy-phenoxy)-3,6-dimethyl-pyridin-4-yl]-amine
 1H NMR(CDCl₃) d 6.90 (s, 2H), 6.09 (s, 1H), 3.78 (d, 1H, J=8Hz), 3.45-3.52 (m, 1H),
 2.15 (s, 3H), 2.10 (s, 9H), 1.51-1.67 (m, 2H), 1.23 (d, 3H, J=8Hz), 0.98 (t, 3H, J=7 Hz) ppm.

Example 296

20 [2-(2,6-Dimethyl-4-trifluoromethoxy-phenoxy)-3,6-dimethyl-pyridin-4-yl]-(1-ethyl-propyl)-amine
 1H NMR(CDCl₃) d 6.91 (s, 2H), 6.08 (s, 1H), 3.74 (d, 1H, J=8Hz), 3.31-3.34 (m, 1H),
 2.15 (s, 3H), 2.11 (s, 6H), 2.08 (s, 3H), 1.49-1.68 (m, 4H), .96 (t, 6H, J=8Hz) ppm.

Example 297

25 [3,6-Dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-(2-pyrrolidin-1-yl-ethyl)-(2,2,2-trifluoro-ethyl)-amine
 1H NMR(CDCl₃) d 6.87 (s, 2H), 6.55 (s, 1H), 3.78 (q, 2H, J=9Hz), 3.60-3.72 (m, 2H),
 2.82-2.98 (m, 6H), 2.29 (s, 3H), 2.26 (s, 3H), 2.20 (s, 3H), 2.03 (s, 6H), 1.96 (br s, 4H) ppm.

The following compounds (Examples 298 and 299) were prepared starting with an appropriate 2-(substituted-phenoxy)-4-(1-methanesulfonyloxyethyl-propylamino)-3,6-substituted-pyridine with an appropriate amine:

Example 298

N2-[2-(4-Chloro-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridin-4-yl]-N1-cyclopropylmethyl-butane-1,2-diamine
 1H NMR(CDCl₃) d 7.01(s, 2H), 6.17(s, 1H), 4.40(d, 1H), 3.82(m, 1H), 3.05(m, 2H),
 2.69(m, 2H), 2.20(s, 3H), 2.12(s, 3H), 2.04(s, 6H), 1.70(m, 2H), .98(t, 3H), .96(m, 4H) ppm

-100-

Example 299

N-[3,6-Dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-N-ethyl-N',N'-dimethyl-ethane-1,2-diamine

5 1H NMR(CDCl₃) d 6.86(s, 2H), 6.43 (s, 1H), 3.26 (AB quartet, 2H), 3.12 (q, 2H, J=7Hz), 2.51 (AB quartet, 2H), 2.34 (s, 6H), 2.29 (s, 3H), 2.23 (s, 3H), 2.18 (s, 3H), 2.05 (s, 6H), 1.09 (t, 3H, J=7 Hz) ppm.

Example 300

N-2-[3,6-Dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-N-1-methyl-butane-1,2-diamine

10 1HNMR(CDCl₃) 6.85(s, 2H), 6.12(s, 1H), 4012(d, 1H), 3.56(m, 1H), 2.79(m, 2H), 2.47(s, 3H), 2.28(s, 3H), 2.14(d, 6H), 2.06(s, 6H), 1.62(m, 2H), 0.97(t, 3H)ppm

Example 301

N-2-[3,6-Dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-N-1-ethyl-butane-1,2-diamine

15 1H NMR(CDCl₃) d 7.80(s, 1H), 6.85(s, 2H), 6.12(s, 1H), 4.22(d, 1H), 3.57(m, 1H), 2.82(m, 2H), 2.72(q, 2H), 2.28(s, 3H), 2.13(s, 6H), 2.06(s, 6H), 1.63(m, 2H), 1.16(t, 3H), 0.97(t, 3H)ppm

Example 302

N2-[3,6-Dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-N1-ethyl-N1-methyl-butane-1,2-diamine

20 1H NMR (CDCl₃) d 6.85(s ,2H), 6.06(s, 1H), 4.58(m, 1H), 3.39(m, 1H), 2.49(m, 4H), 2.28(s, 6H), 2.14(s, 6H), 2.06(s, 6H), 1.66(m, 2H), 1.08(m, 3H), 0.96(t, 3H)ppm

Example 303

N-1-Butyl-N-2-[3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-butane-1,2-diamine

25 1H NMR(CDCl₃) d 6.85(s, 2H), 6.11(s, 1H), 4.21(d, 1H), 3.51(q, 1H), 2.79(m, 2H), 2.65(t, 2H), 2.28(s, 3H), 2.14(s, 6H), 2.06(s, 6H), 1.62(m, 2H), 1.49(m, 2H), 1.35(m, 2H), 0.97(t, 3H), 0.91(t, 3H)ppm

Example 304

N-1-Cyclopropylmethyl-N-2-[3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-N1-propyl-butane-1,2-diamine

30 1H NMR (CDCl₃) d 6.85(s, 2H), 6.06(s, 1H), 4.65(m, 1H), 3.32(m 1H), 2.61(m, 4H), 2.28(s, 3H), 2.14(s,3H), 2.12(s, 2H), 2.06(s, 6H), 1.71(m, 2H), 1.46(m, 2H), 0.96(t, 3H), 0.87(t, 3H)ppm

Example 305N-2-[3,6-Dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-N-1-propyl-butane-1,2-diamine

1H NMR(CDCl₃) d 6.85(s, 2H), 6.11(s, 1H), 4.21(d, 1H), 3.051(q, 1H), 2.79(m, 2H),
5 2.62(m, 2H), 2.28(s, 3H), 2.13(s, 6H), 2.06(s, 6H), 1.62(m, 2H), 1.54(m, 2H), 0.97(t, 3H),
0.91(t, 3H)ppm

Example 306N-2-[3,6-Dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-N-1-(2-methoxy-ethyl)-butane-1,2-diamine

10 1H NMR (CDCl₃) d 6.85(s, 2H), 6.11(s, 1H), 4.18(d, 1H), 3.51(m, 3H), 3.35(s, 2H),
2.82(m, 4H), 2.28(s, 3H), 2.14(s, 6H), 2.06(s, 6H), 1.62(m, 2H), 0.97(t, 3H)ppm

Example 307N-2-[3,6-Dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-N-1-furan-2-ylmethyl-butane-1,2-diamine

15 1HNMR(CDCl₃) 7.36(s, 1H), 6.85(s, 2H), 6.32(d, 1H), 6.24(d, 1H), 6.09(s, 1H),
4.15(d, 1H), 3.84(d, 2H), 3.58(m 1H), 2.79(m, 2H), 2.28(s, 3H), 2.13(d, 6H), 2.05(s, 6H),
1.62(m, 2H), 0.95(t, 3H)ppm

Example 308N-1-Cyclopropylmethyl-N-2-[3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-butane-1,2-diamine

20 1HNMR(CDCl₃) 6.85(s, 2H), 6.14(s, 1H), 4.39(m, 1H), 3.70(m, 1H), 3.01(m, 2H),
2.67(d, 2H), 2.28(s, 3H), 2.20(s, 3H), 2.14(s, 3H), 2.05(s, 6H), 1.71(m, 2H), 0.98(t, 3H),
0.55(d, 2H), 0.21(d, 2H)ppm.

Example 309[3,6-Dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-(1-thiazolidin-3-ylmethyl)-propyl)-amine

25 1HNMR(CDCl₃) 6.85(s, 2H), 6.07(s, 1H), 4.21(d, 1H), 4.06(d, 2H), 3.41(m, 1H),
3.07(m, 2H), 2.89(m, 2H), 2.52(m, 2H), 2.28(s, 3H), 2.15(d, 6H), 2.06(s, 6H), 1.75(m, 1H),
1.66(m, 1H), 0.98(t, 3H)ppm

Example 310N-2-[3,6-Dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-butane-1,2-diamine

To a solution of (1-hydroxymethyl-propyl)-[3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-amine in toluene was added diphenylphosphoryl azide and 1,8-diazabicyclo[3.4.0]undec-7-ene at 0°C. The resulting mixture was stirred at rt for 30min, then
35 heated 75°C overnight. The reaction mixture was quenched with water and extracted with methylene chloride. The organic layer was separated, dried, concentrated and purified by

silica gel Biotage using 1:1 methylene chloride/hexane to methylene chloride as eluent to give (1-azidomethyl-propyl)-[3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-amine as a light yellow oil. The oil was reduced with triphenylphosphine to give the title compound. ^1H NMR (CDCl_3) δ 6.86(s, 2H), 6.11(s, 1H), 4.02(d, 1H), 3.40(q, 1H), 2.84(m, 2H), 2.28(s, 3H), 2.13(s, 6H), 2.06(s, 6H), 1.61(m, 2H), 0.98(t, 3H) ppm

Example 311

1-[2-[3,6-Dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-ylamino]-butyl]-3-ethyl-urea

A mixture of N-2-[3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-butane-1,2-diamine and ethyl isocyanate in dichloroethane was stirred at rt overnight. Standard work-up and purification yielded the title compound. APCI [M+1] = 399.3, ^1H NMR(CDCl_3)

Example 312

N-[2-[3,6-Dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-ylamino]-butyl]-methanesulfonamide

A mixture of N-2-[3,6-Dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-butane-1,2-diamine and methanesulfonyl chloride in dichloroethane was stirred at rt overnight. Standard work-up and purification yielded the title compound. APCI [M+1] = 406.2, ^1H NMR(CDCl_3)

Example 313

N-[2-[3,6-Dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-ylamino]-butyl]-acetamide

A mixture of N-2-[3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-butane-1,2-diamine and acetyl chloride in dichloroethane was stirred at rt overnight. Standard work-up and purification yielded the title compound. APCI [M+1] = 370.3, ^1H NMR(CDCl_3)

Example 314

Cyclopropylmethyl-[3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-propyl-amine

1H NMR(CDCl_3) δ 6.85 (s, 2H), 6.44 (s, 1H), 3.13 (AB q, 2H), 2.90 (d, 2H, $J=8$ Hz), 2.28 (s, 3H), 2.24 (s, 3H), 2.16 (s, 3H), 2.05 (s, 6H), 1.47-1.65 (m, 2H), 0.86-0.92 (m, 4H), 0.42-0.46 (m, 2H), 0.04-0.08 (m, 2H)

APCI+ m/z = 353.3 (M+1)

Example 315

Cyclopropylmethyl-[3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-propyl-amine

1H NMR(CDCl_3) δ 6.85 (s, 2H), 6.44 (s, 1H), 3.13 (AB q, 2H), 2.90 (d, 2H, $J=8$ Hz), 2.28 (s, 3H), 2.24 (s, 3H), 2.16 (s, 3H), 2.05 (s, 6H), 1.47-1.65 (m, 2H), 0.86-0.92 (m, 4H), 0.42-0.46 (m, 2H), 0.04-0.08 (m, 2H)

APCI+ m/z = 353.3 (M+1)

Example 3163,6-Dimethyl-4-(2-methyl-aziridin-1-yl)-2-(2,4,6-trimethyl-phenoxy)-pyridine

1H NMR(CDCl₃) d 6.86 (s, 2H), 6.29 (s, 1H), 2.31 (sa, 3H), 2.29 (s, 3H), 2.19 (m, 1H), 2.15 (s, 3H), 2.10 (m, 2H), 2.04 (s, 6H), 1.44 (d, 3H, J=5 Hz)

5

Example 3174-(2-Methoxymethyl-pyrrolidin-1-yl)-3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridine

1H NMR(CDCl₃) d 6.86 (s, 2H), 6.34 (s, 1H), 3.99 (q, 1H, J = 4Hz), 3.67 (m, 1H), 3.49 (dd, 1H, J=9 Hz, 4 Hz), 3.32 (s, 3H), 3.15 (m, 2H) 2.29 (s, 3H), 2.24 (s, 3H), 2.16 (s, 3H), 2.06 (s, 6H), 1.78-1.97 (m, 4H) ppm.

10

Example 318[2-(4-Chloro-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridin-4-yl]-[tetrahydro-furan-3-yl]-amine

1H NMR(CDCl₃) d 7.04(s,2H), 6.11(s,1H), 4.27(brs,1H), 3.7-4.1(m,4H), 2.2-2.4(m,1H), 2.08(s,6H), 2.07(s,6H), 1.94(m,1H) ppm.

15

Example 319[1-(tert-Butyl-dimethyl-silyloxyethyl)-propyl]-[3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-amine

1H NMR(CDCl₃) d 6.85(s, 2H), 6.07(s, 1H), 3.71(m, 2H), 3.39(m, 1H), 2.28(s, 3H), 2.16(s, 3H), 2.09(s, 3H), 2.06(s, 6H), 1.70(m, 2H), 0.91(s 9H)ppm

20

Example 320[3,6-Dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-ethyl-(2-pyrrolidin-1-yl-ethyl)-amine

1H NMR(CDCl₃) d 6.86 (s, 2H), 6.44 (s, 1H), 3.25-3.30 (m, 2H), 3.12 (q, 2H, J=7Hz), 2.56-2.66 (m, 6H), 2.29 (s, 3H), 2.23 (s, 3H), 2.17 (s, 3H), 2.05 (s, 6H), 1.80 (br s, 4H), 1.09

25 (t, 3H, J=7Hz)

13C NMR(CDCl₃) d.

APCI+ m/z = 382(M+1)

Example 3214-[4-(1-Ethyl-propoxy)-3,6-dimethyl-pyridin-2-yloxy]-3,5-dimethyl-benzoic acid

30 To a -78°C solution of intermediate in dry THF was added n-BuLi. After stirring at that temperature for 10 min, CO₂(g) was bubbled into the reaction mixture. The resulting mixture was stirred at -78°C for 2 hr, gradually warmed to rt. The mixture was quenched with dilute HCl and extracted with methylene chloride. The organic layer was separated, dried, concentrated, and purified to give the title compound as a white solid, mp. 168.4°C.

35 NMR(CDCl₃) 7.58(s,2H), 6.36(s,1H), 4.24(m,1H), 2.35(s,3H), 2.22(s,3H), 2.14(s,6H), 1.75(m,4H), 0.99(t,6H) ppm.

The following Examples 322-326 were prepared according to the following general procedure: To a solution of 4-[4-(1-ethyl-propoxy)-3,6-dimethyl-pyridin-2-yloxy]-3,5-dimethylbenzoic acid in anhydrous methylene chloride was added SOCl_2 and stirred at rt. for 1 hr. the mixture was concentrated to dryness to provide the corresponding acyl chloride. The acyl chloride was quenched with an appropriate nucleophile (e.g., NH_3 , MeNH_2 , Me_2NH , EtNH_2 , or methanol) and stirred at rt to provide the title compounds:

Example 322

4-[4-(1-Ethyl-propoxy)-3,6-dimethyl-pyridin-2-yloxy]-3,5-dimethyl-benzamide

1H NMR(CDCl_3) d 7.51(s,2H), 6.32(s,1H), 6.2(brs,1H), 5.7(brs,1H), 4.20(m,1H),
10 2.22(s,3H), 2.19(s,3H), 2.12(s,6H), 1.72(m,4H), 0.97(t,6H) ppm.

Example 323

4-[4-(1-Ethyl-propoxy)-3,6-dimethyl-pyridin-2-yloxy]-3,5,N-trimethyl-benzamide

1H NMR(CDCl_3) d 7.43(s,2H), 6.30(s,1H), 6.19(brs,1H), 4.19(m,1H), 2.95(d,3H),
2.19(s,3H), 2.18(s,3H), 2.10(s,6H), 1.71(m,4H), 0.97(t,6H) ppm.

Example 324

4-[4-(1-Ethyl-propoxy)-3,6-dimethyl-pyridin-2-yloxy]-3,5,N,N-tetramethyl-benzamide

1H NMR(CDCl_3) d 7.12(s,2H), 6.30(s,1H), 4.18(m,1H), 3.09(s,3H), 3.05(s,3H),
2.18(s,6H), 2.10(s,6H), 1.71(m,4H), 0.97(t,6H) ppm.

Example 325

N-Ethyl-4-[4-(1-ethyl-propoxy)-3,6-dimethyl-pyridin-2-yloxy]-3,5-dimethyl-benzamide

1H NMR(CDCl_3) d 7.46(s,2H), 6.30(s,1H), 6.1(brs,1H), 4.19(m,1H), 3.48(m,2H),
2.18(s,6H), 2.12(s,6H), 1.72(m,4H), 1.25(t,3H), 0.97(t,6H) ppm.

Example 326

4-[4-(1-Ethyl-propoxy)-3,6-dimethyl-pyridin-2-yloxy]-3,5-dimethyl-benzoic acid methyl

ester

1H NMR(CDCl_3) d 7.76(s,2H), 6.30(s,1H), 4.17(m,1H), 3.89(s,3H), 2.19(s,3H),
2.169(s,3H), 2.12(s,6H), 1.712(m,4H), 0.97(t,6H) ppm.

The following Examples 327-329 were prepared by the following general procedure: To a solution of 4-[4-(1-Ethyl-propylamino)-3,6-dimethyl-pyridin-2-yloxy]-3,5-dimethylbenzoic acid in anhydrous methylene chloride was added SOCl_2 and stirred at rt for 1 hr. the mixture was concentrated to dryness to provide the corresponding acyl chloride. The acyl chloride was quenched with an appropriate nucleophile (e.g., NH_3 , MeNH_2 , or methanol) and stirred at rt to provide the title compounds:

Example 3274-[4-(1-Ethyl-propylamino)-3,6-dimethyl-pyridin-2-yloxy]-3,5-dimethyl-benzamide

1H NMR(CDCl₃) d 7.51(s,2H), 6.2(brs,1H), 6.1(s,1H), 5.5(brs,1H), 3.9(d,1H), 3.3(m,1H), 2.19(s,3H), 2.14(s,6H), 2.12(s,3H), 1.7(m,2H), 1.5(m,2H), 0.96(t,6H) ppm.

5

Example 3284-[4-(1-Ethyl-propylamino)-3,6-dimethyl-pyridin-2-yloxy]-3,5,N-trimethyl-benzamide

1H NMR(CDCl₃) d 7.431(s,2H), 6.3(ds,1H), 6.091(s,1H), 3.8(d,1H), 3.35(m,1H), 2.96(d,3H), 2.16 (s,3H), 2.12(s,9H), 1.65(m,2H), 1.53(m,2H), 0.95(t,6H) ppm.

10 4-[4-(1-Ethyl-propylamino)-3,6-dimethyl-pyridin-2-yloxy]-3,5-dimethyl-benzoic acid methyl ester

1H NMR(CDCl₃) d 7.751(s,2H), 6.08(s,1H), 3.89(s,3H), 3.80(d,1H), 3.34(m,1H), 2.13(s,6H), 2.11(s,6H), 1.66(m,2H), 1.54(m,2H), 0.95(t,6H) ppm.

15 The following Examples 330-340 relate to other compounds of formula I of the invention, wherein R₄ is -CN:

Example 3302-(4-Chloro-2,6-dimethyl-phenoxy)-6-methyl-4-(tetrahydro-furan-3-ylamino)-nicotinonitrile

APCI [M+1] 358.3

20 Example 331

4-(1-Ethyl-propylamino)-2-(4-methoxy-2,6-dimethyl-phenoxy)-6-methyl-nicotinonitrile

Cala: C: 71.36; H: 7.70; N:11.89; found: C: 71.16, H: 8.09, N: 11.47; HNMR(CDCl₃) 6.59(s, 2H), 6.08(s, 1H), 4.74(d, 1H), 3.78(s, 3H), 3.38(m, 1H), 2.18(s, 3H), 2.10(s, 6H), 1.64(m, 2H), 1.55(m, 2H), 0.96(t, 6H)ppm.

25 Example 332

4-(1-Ethyl-propylamino)-6-methyl-2-(2,4,6-trimethyl-pyridin-3-yloxy)-nicotinonitrile

The title compound was prepared by heating 2-chloro-4-(1-ethyl-propylamino)-6-methyl-nicotinonitrile with 2,4,6-trimethyl-3-hydroxy-pyridine in NMP.

1HNMR(CDCl₃) 7.02(m,1H), 6.13(s, 1H), 4.81(d, 1H), 3.40(m, 1H), 2.67(s, 3H), 2.48(s, 3H), 2.25(s, 3H), 2.16(s, 3H), 1.68(m, 4H), 0.97(t, 6H)ppm

Example 3332-(4-Methoxy-2,6-dimethyl-phenoxy)-4-(1-methoxymethyl-propylamino)-6-methyl-nicotinonitrile

1HNMR(CDCl₃) 6.59(s, 2H), 6.11(s, 1H), 5.08(d, 1H), 3.78(s, 3H), 3.56(m, 1H), 3.47(m, 1H), 3.38(s, 3H), 2.19(s, 3H), 2.10(s, 6H), 1.61(m, 2H), 0.99(t, 3H) ppm

Example 3342-(4-Bromo-2,6-dimethyl-phenoxy)-4-(1-ethyl-propylamino)-6-methyl-nicotinonitrile

1H NMR(CDCl₃) d 7.19(s,2H), 6.09(s,1H), 4.77(d,1H), 3.39(m,1H), 2.18(s,3H), 2.10(s,6H), 1.65(m,2H), 1.55(m,2H), 0.96(t,3H) ppm.

5

Example 3354-[3-Cyano-4-(1-ethyl-propylamino)-6-methyl-pyridin-2-yloxy]-3-methoxy-benzoic acid methyl ester

APCI [M+1] 384.2, 1H NMR(CDCl₃)

Example 336

10 4-[3-Cyano-4-(1-ethyl-propylamino)-6-methyl-pyridin-2-yloxy]-3-methoxy-benzamide
 1H NMR(CDCl₃) d 7.52(s,1H), 7.32(d,1H), 7.16(d,1H), 6.25(brs,1H), 6.12(s,1H), 5.8(brs,1H), 4.78(d,1H), 3.80(s,3H), 3.39(m,1H), 2.20(s,3H), 1.67(m,2H), 1.55(m,2H), 0.95(t,3H) ppm.

15

Example 3372-(4-Chloro-2,6-dimethyl-phenoxy)-4-(1-methoxymethyl-propylamino)-6-methyl-nicotinonitrile

1H NMR(CDCl₃) d 7.03(s,2H), 6.12(s,1H), 5.08(d,1H), 3.47(m,1H), 3.43(m,2H), 3.38(s,3H), 2.18(s,3H), 2.09(s,6H), 1.76(m,2H), 1.61(m,2H), 0.99(t,6H) ppm.

20

Example 3382-(4-Chloro-2,6-dimethyl-phenoxy)-4-[(1-methoxymethyl-propyl)-methyl-amino]-6-methyl-nicotinonitrile
 1H NMR(CDCl₃) d 7.03(s,2H), 6.27(s,1H), 4.33(m,1H), 3.59(m,1H), 3.52(m,1H), 3.35(s,3H), 3.06(s,3H), 2.16(s,3H), 2.11(s,6H), 1.69(m,4H), 0.97(t,6H) ppm..

25

Example 3392-(4-Chloro-2-methoxy-phenoxy)-4-(1-ethyl-propylamino)-6-methyl-nicotinonitrile
 1H NMR(CDCl₃) d 7.04 (d, 1H, J=9 Hz), 6.91-6.94 (m, 2H), 6.10 (s, 1H), 4.73 (d, 1H, J=9 Hz), 3.75 (s, 3H), 3.35-3.38 (m, 1H), 2.19 (s, 3H), 1.47-1.70 (m, 4H), 0.95 (t, 6H, J=8 Hz)
 APCI+ m/z = 360.1 (M+1), 362.1 (M+3)

30

Example 3402-(4-Bromo-2-methoxy-phenoxy)-4-(1-ethyl-propylamino)-6-methyl-nicotinonitrile
 1H NMR(CDCl₃) d 7.06-7.09 (m, 2H), 6.98-7.00 (m, 1H), 6.10 (s, 1H), 4.73 (br d, 1H), 3.75 (s, 3H), 3.35-3.42 (m, 1H), 2.21 (s, 3H), 1.43-1.72 (m, 4H), 0.95(t, 6H, J=7 Hz) ppm.

Other examples of compounds of the invention are as follows:

Example 341[2-(4-Chloro-2,6-dimethyl-phenoxy)-6-methyl-pyridin-4-yl]-(1-methoxymethyl-propyl)-amine

5 1H NMR(CDCl₃) δ 7.05 (s, 2H), 6.04 (s, 1H), 5.33 (s, 1H), 4.26 (br d, 1H), 3.34-3.39
(m, 1H), 3.31 (s, 6H), 2.31 (s, 3H), 2.12 (s, 6H), 1.47-1.61 (m, 4H), 0.89 (t, 6H, J=8Hz) ppm.

Example 342[2-(4-Chloro-2,6-dimethyl-phenoxy)-6-methyl-3-methylaminomethyl-pyridin-4-yl]-(tetrahydro-furan-3-yl)-amine

10 1H NMR(CDCl₃) δ 7.03(s,2H), 6.08(s,1H), 4.18(s,2H), 3.8-4.2(m,5H), 2.57(s,3H), 2.2-
2.4(m,2H), 2.15(s,3H), 2.04(s,6H) ppm.

Example 343[2-(4-Chloro-2,6-dimethyl-phenoxy)-6-methyl-4-(tetrahydro-furan-3-ylamino)-pyridin-3-yl]-methanol

15 1H NMR(CDCl₃) δ 7.02(s,2H), 6.10(s,1H), 5.49(brs,1H), 4.89(t,2H), 4.12(brs,1H),
4.01(m,2H), 3.99(m,1H), 3.75(m,1H), 2.30(m,1H), 2.16(s,3H), 2.05(s,6H), 1.95(m,1H) ppm.

Example 3442-[2-(4-Chloro-2,6-dimethyl-phenoxy)-6-methyl-pyridin-4-ylamino]-4-methylsulfanyl-butani-1-ol

20 1H NMR(CDCl₃) δ 7.06(s,2H), 6.29(s,1H), 5.47(s,1H), 3.6-3.8(m,2H), 3.5(m,1H),
2.38(s,3H), 2.11(s,6H), 2.03(s,3H), 1.87(m,1H), 1.69(m,1H) ppm.

Preparation A(6-Chloro-2-methyl-5-nitro-pyrimidin-4-yl)-(2,4,6-trimethyl-pyridin-3-yl)-amine

A solution of 2-methyl-5-nitro-4,6-dichloro-pyrimidine (208 mg, 1.00 mmol) in 2.5 ml of acetonitrile was treated with 2,4,6-trimethyl-3-amino-pyridine (273 mg, 2 mmol) stirred at room temperature 2 hours. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was washed with brine, dried and concentrated to give red residue. The residue was purified through silica gel column chromatography using chloroform to 6% methanol in chloroform as eluent to give the title compound (110 mg, 36%) as an orange oil. ¹H NMR (CDCl₃) δ 8.78 (brs, 1H), 6.97 (s, 1H), 2.54 (s, 3H), 2.43 (s, 3H), 2.40 (s, 3H), 2.17 (s, 3H)
30 ppm.

Preparation B2-Chloro-4-(1-ethyl-propylamino)-6-methyl-nicotinic acid

The title compound was prepared by reaction of 2-chloro-4-(1-ethyl-propylamino)-6-methyl-nicotinic acid methyl ester with LiOH.H₂O in a mixture of water and dioxane at room temperature. The desired product was acidified to pH 3 and extracted with ethyl acetate. The organic layer was dried and concentrated to dryness. The title compound was obtained as
35

white crystals after titration with ethyl acetate. mp. 164-165°C; anal. For $C_{12}H_{17}Cl_2O_2$ calc. C, 56.14; H, 6.67; N, 10.91; found: C, 56.40; H, 6.53; N, 10.93.

Preparation C

4-Chloro-6-ethyl-3-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridine 1-oxide

5 To a solution of 2,4,6-trimethylphenol in dry THF was added NaH and stirred at room temperature for 20 minutes. A solution of 2,4-dichloro-6-ethyl-3-methyl-pyridine 1-oxide was added and the resulting mixture was heated at reflux for 1.5 hour. The mixture was cooled to room temperature, quenched with water, extracted with ethyl acetate. The organic layer was separated, dried and concentrated to give the title compound which was used directly for the
10 next step reaction.

Preparation D

4-Chloro-6-ethyl-3-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridine

To a solution of 4-Chloro-6-ethyl-3-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridine 1-
15 oxide in methylene chloride was added PCl_3 and the resulting mixture was heated at reflux for
20 min, cooled to rt. The mixture was concentrated to dryness. The residue was worked-up
using standard procedure to give the title compound. After silica gel purification, the title
compound was prepared as a white solid, mp. 42-44°C. Anal. For $C_{17}H_{20}ClNO$ calc. C, 70.46;
H, 6.96; N, 4.83; found, C, 70.35; H, 7.13; N, 4.58.

Preparation E

20 2-[4-Chloro-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-3-ylmethyl]-malonic acid
dimethyl ester

The title compound was prepared by reacting 4-chloro-3-chloromethyl-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridine with dimethyl malonate/NaH in methanol. The title compound was isolated as a colorless oil.

25 Preparation F

4-Chloro-3,6-dimethyl-2-(2,4,6-trimethyl-3-pyridyl)-pyridine

Preparation G

2-Chloro-4-(1-methoxymethyl-propoxy)-6-methyl-nicotinic acid ethyl ester

1H NMR($CDCl_3$) d 6.72(s,1H), 4.5(m,1H), 4.4(q,2H), 3.49(d,2H), 3.31(s,3H),
30 2.46(s,3H), 1.68(m,2H), 1.34(t,3H), 0.93(t,3H) ppm.

Preparation H

2-Chloro-4-(1-methoxymethyl-propoxy)-6-methyl-nicotinic acid

1H NMR($CDCl_3$) d 6.81(s,2H), 4.51(m,1H), 3.60(m,2H), 3.40(s,3H), 2.55(s,3H),
1.77(m,2H), 1.02(t,3H)ppm.

Preparation I(2-Chloro-6-methyl-3-nitro-pyridin-4-yl)-(1-methoxymethyl-propyl)-aminemp. 63-65°C; Anal. For C₁₁H₁₆N₃O₃Cl calc. C, 48.27; H, 5.89, N, 15.35; found C,

48.65; H, 6.03, N, 15.11.

5

Preparation J(5-Bromo-6-chloro-2-methyl-pyrimidin-4-yl)-(2,4-dichloro-phenyl)-amineMp. 165-167°C; Anal. For C₁₁H₇BrCl₃ calc.: C, 35.95; H, 1.92; N, 11.43; found: C,

36.41; H, 1.91; N, 11.05.

10

Preparation K(6-Chloro-2-methyl-pyrimidin-4-yl)-(2,4-dichloro-phenyl)-amineMp. 134-136°C; Anal. For C₁₁H₈Cl₃N₃ calc.: C, 45.79; H, 2.79; N, 14.56; found: C,

45.91; H, 2.69; N, 14.50.

Preparation L[4-Chloro-6-(1-ethyl-propylamino)-2-methyl-pyrimidin-5-yl]-acetic acid ethyl ester

15

Mp. 78-80°C, anal. For C₁₄H₂₂ClN₃O₂ calc.: C, 56.09; H, 7.40; N, 14.02; found: C,

56.31; H, 7.60; N, 13.94.

Preparation M2-[4-Bromo-2-methyl-6-(2,4,6-trimethyl-phenoxy)-pyrimidin-5-yl]-propionic acid ethyl ester

20

1H NMR(CDCl₃) d 6.86(s,2H), 4.2-4.359m,2H), 4.0-4.15(m,1H), 2.4(s,3H), 2.28(s,3H), 1.99(s,3H), 1.97(s,3H), 1.58(d,3H), 1.22(t,3H) ppm.Preparation N2-(4,6-Dibromo-2-methyl-pyrimidin-5-yl)-propionic acid ethyl ester1H NMR(CDCl₃) 4.36(m,1H), 4.19(m,2H), 2.68(s,3H), 1.549d,3H), 1.22(t,3H) ppm.

25

Preparation O4-Bromo-3-methoxy-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridine1H NMR(CDCl₃) d 6.92(s,1H), 6.87(s,2H), 4.00(s,3H), 2.299s,3H), 2.18(s,3H), 2.059s,6H) ppm.Preparation P

30

4-Bromo-2-(4-chloro-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridine1H NMR(CDCl₃) d 7.04(s,2H), 6.97(s,1H), 2.42(s,3H), 2.17(s,3H), 2.03(s,6H) ppm.Preparation Q4-Bromo-2-(2,4-dichloro-6-methyl-phenoxy)-3-methoxy-6-methyl-pyridine1H NMR(CDCl₃) d 7.3(d,1H), 7.18(d,1H), 4.0(s,3H), 2.2(s,3H), 2.15(s,3H) ppm.

Preparation R4-Bromo-2-(4-chloro-2,6-dimethyl-phenoxy)-3-methoxy-6-methyl-pyridine

Anal. For C₁₅H₁₅BrClNO₂ calc.: C, 50.52; H, 4.24; N, 3.93; found: C, 50.52; H, 4.37; N, 3.91.

5

Preparation S4-Bromo-2-(4-chloro-2-methoxy-phenoxy)-3-methoxy-6-methyl-pyridine

1H NMR(CDCl₃) d 6.9-7.1(m,4H), 3.94(s,3H), 3.71(s,3H), 2.21s,3H) ppm.

Preparation T4-Bromo-2-(3-chloro-2,6-dimethoxy-phenoxy)-3-methoxy-6-methyl-pyridine

10 1H NMR(CDCl₃) d 7.17(d,1H), 6.96(s,1H), 6.66(d,1H), 3.97(s,3H), 3.79(s,3H), 3.70(s,3H), 2.18(s,3H) ppm.

Preparation U4-Bromo-3-methoxy-6-methyl-2-(2,4,6-trimethoxy-phenoxy)-pyridine

15 1H NMR(CDCl₃) d 6.90(s,1H), 6.19(s,2H), 3.968(s,3H), 3.80(s,3H), 3.71(s,6H), 2.18(s,3H) ppm.

Preparation V4-Bromo-3-methoxy-2-(4-methoxy-2,6-dimethyl-phenoxy)-6-methyl-pyridine

20 1H NMR(CDCl₃) d 6.92(s,1H), 6.60(s,2H), 3.98(s,3H), 3.78(s,3H), 2.18(s,3H), 2.07(s,6H) ppm.

20

Preparation W4-Bromo-2-(4-chloro-2,6-dimethyl-phenoxy)-3-ethoxy-6-methyl-pyridine

25 1H NMR(CDCl₃) d 7.099s,2H), 7.00(s,1H), 4.28(q,2H), 2.22(s,3H), 2.10(s,6H), 1.51(t,3H) ppm.

Preparation X4-Bromo-3,6-dimethyl-2-(2,4,6-trimethoxy-phenoxy)-pyridine

1H NMR(CDCl₃) d 6.99(s,1H), 6.25(s,2H), 3.86(s,3H), 3.77(s,6H), 2.47(s,3H), 2.25(s,3H) ppm.

Preparation Y4-Chloro-2-(4-chloro-2,6-dimethyl-phenoxy)-6-methyl-1-oxy-nicotinic acid methyl ester30 esterPreparation RR4-Chloro-2-(4-chloro-2,6-dimethyl-phenoxy)-6-methyl-nicotinic acid methyl ester

1H NMR(CDCl₃) d 7.03(s,2H), 6.869s,1H), 3.969s,3H), 2.259s,3H), 2.05(s,6H) ppm.

Preparation Z4-Chloro-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridine-3-carbaldehyde

The title compound was prepared by oxidation of 4-chloro-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-3-yl-methanol with pyridinium chlorochromate in methylene chloride at room temperature. The desired product was isolated after column chromatography to give a green solid (80% yield). 1H NMR(CDCl₃) δ 10.66(s,1H), 6.91(s,3H), 2.31(s,3H), 2.07(s,3H) ppm.

Preparation AA2-(4-Bromo-2,6-dimethyl-phenoxy)-4-chloro-6-methyl-nicotinic acid methyl ester

mp. 108-110°C; Anal. For C₁₆H₁₅BrClNO₃ calc., 49.96; H, 3.93; N, 3.64; found: C, 10 50.07; H, 4.10; N, 3.57.

Preparation BB4-Chloro-2-(4-chloro-2-methoxy-phenoxy)-6-methyl-1-oxy-nicotinic acid methyl ester

mp. 117-120°C, Anal. For C₁₅H₁₃NO₅Cl₂ calc.: C, 50.30; H, 3.66; N, 3.91; Found: C, 15 50.41; H, 3.55; N, 4.00.

Preparation CC4-Chloro-2-(4-chloro-2-methoxy-phenoxy)-6-methyl-nicotinic acid methyl ester

mp. 92-93°C, Anal. For C₁₅H₁₃NO₄Cl₂ calc.: C, 52.65; H, 3.83; N, 4.09; found: C, 15 52.34; H, 3.85; N, 4.13.

Preparation DD

20 [1-(tert-Butyl-dimethyl-silanyloxymethyl)-propyl]-[2-(4-chloro-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridin-4-yl]-amine

1H NMR(CDCl₃) δ 7.06(s,2H), 6.12(s,1H), 4.3(d,1H), 3.6-3.8(m,2H), 3.4(m,1H), 2.16(s,3H), 2.14(s,3H), 2.10(s,6H), 1.5-1.8(m,2H), 1.03(t,3H), 0.95(s,9H), 0.09(m,6H) ppm.

The following compounds were prepared by a method analogous to that described in 25 Example 160, using an appropriate 4-bromo-2-(substituted phenoxy)-6-alkyl or alkoxy-pyridine with 1-(tert-Butyl-dimethyl-silanyloxymethyl)-propylamine.

Preparation EE

[1-(tert-Butyl-dimethyl-silanyloxymethyl)-propyl]-[3-methoxy-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-(S)-yl]-amine

30 1H NMR (CDCl₃) δ 6.84(s,2H), 6.08(s,1H), 4.8(d,1H), 3.88(s,3H), 3.5-3.7(m,2H), 3.3(m,1H), 2.27(s,3H), 2.099(s,3H), 2.07(s,6H), 1.75(m,1H), 1.55(m,1H), 0.97(t,3H), 0.89(s,9H), 0.04(s,6H) ppm.

Preparation FF

[1-(tert-Butyl-dimethyl-silanyloxymethyl)-propyl]-[2-(4-chloro-2,6-dimethyl-phenoxy)-3-methoxy-6-methyl-pyridin-4-yl]-amine

5 1H NMR(CDCl₃) d 7.02(s,2H), 6.10(s,1H), 4.80(d,1H), 3.87(s,3H), 3.6-3.7(m,2H),
3.30(m,1H), 2.09(s,3H), 2.08(s,6H), 1.75(m,1H), 1.55(m,1H), 0.97(t,3H), 0.89(s,9H),
0.03(s,6H) ppm.

Preparation GG

4-[1-(tert-Butyl-dimethyl-silanyloxymethyl)-propylamino]-2-(4-chloro-2,6-dimethyl-phenoxy)-6-methyl-pyridin-3-ol

10 1H NMR(CDCl₃) d 7.01 (s,2H), 6.15(s,1H), 4.46(d,1H), 3.7(m,1H), 3.6(m,1H),
3.4(m,1H), 2.09(s,3H), 2.08(s,6H), 1.5-1.8(m,2H), 1.06(s,9H), 0.98(t,3H), 0.24(s,6H) ppm.

Preparation HH

[1-(tert-Butyl-dimethyl-silanyloxymethyl)-propyl]-[3-methoxy-6-methyl-2-(2,4,6-trimethoxy-phenoxy)-pyridin-4-yl]-amine

15 1H NMR(CDCl₃) d 6.19(s,2H), 6.09(s,1H), 3.86(s,3H), 3.80(s,3H), 3.73(s,6H),
3.3(m,1H), 2.16(s,3H), 1.75(m,1H), 1.5(m,1H), 0.95(t,3H), 0.89(s,9H), 0.04(s,6H) ppm.

Preparation II

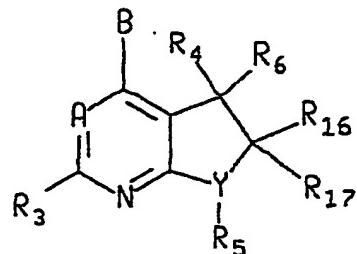
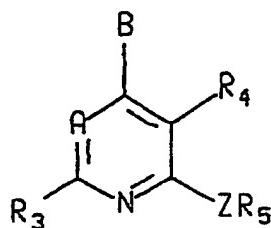
4-[4-[1-(tert-Butyl-dimethyl-silanyloxymethyl)-propylamino]-3-methoxy-6-methyl-pyridin-2-yloxy]-3,5-dimethyl-benzonitrile

20 1H NMR(CDCl₃) d 7.40(s,2H), 6.19(s,1H), 4.90(brs,1H), 3.87(s,3H), 3.70(m,2H),
3.3(m,1H), 2.19(m,9H), 1.5-1.8(m,2H), 1.02(t,3H), 0.93(s,9H), 0.09(s,6H) ppm.

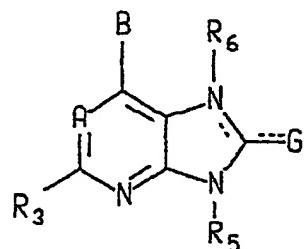
-113-

CLAIMS

1. A compound of the formula



or



or a pharmaceutically acceptable salt thereof, wherein

5 the dashed lines represent optional double bonds, with the proviso that when the dashed line in C—G represent a double bond, then the dashed line in N(R₆)—C does not represent a double bond; and with the proviso that when the dashed line in N(R₆)—C represents a double bond, R₆ is absent in formula III and the dashed line in C—G does not represent a double bond;

10 A is —CR₁ or N;

B is —NR₁R₂, —CR₁R₂R₁₁, —C(=CR₂R₁₂)R₁, —NHCHR₁R₂, —OCHR₁R₂, —SCHR₁R₂, —CHR₂OR₁, —CHR₁OR₂, —CHR₂SR₁, —C(S)R₂, —C(O)R₂, —CHR₂NR₁R₂, —CHR₁NHR₂, —CHR₁N(CH₃)R₂, or —NR₁₂NR₁R₂;

when the dashed line in $C\text{---}G$ represents a double bond, then G is hydrogen, oxygen, sulfur, NH, or N(C₁-C₄ alkyl);

- when the dashed line in $C\text{---}G$ does not represent a double bond, then $C\text{---}G$ is - C(H)(NH₂), CH₂, -C(H)(methoxy), -C(H)(ethoxy), -C(H)(O(C₃-C₄ alkyl)), -C(H)(halo), -C(H)(trifluoromethoxy), -C(H)(methyl), -C(H)(ethyl), -C(H)(C₃-C₄ alkyl), -C(H)(S(C₁-C₄ alkyl)), -C(C₁-C₄ alkyl)(C₁-C₄ alkyl), cyclopropyl, -C(H)(cyclopropyl), thiomethoxy, -C(H)(NH₂), -C(H)(NHCH₃), -C(H)(N(CH₃)₂), or -C(H)(trifluoromethyl);

wherein said cyclopropyl, methoxy, ethoxy, C₃-C₄ alkyl, and C₁-C₄ alkyl groups of $C\text{---}G$ may optionally be substituted by one OH, methoxy, or trifluoromethoxy, or may optionally be substituted by from one to six fluoro atoms;

Y is CH or N;

Z is NH, O, S, -N(C₁-C₂ alkyl), -NC(O)CF₃, or -C(R₁₃R₁₄), wherein R₁₃ and R₁₄ are each, independently, hydrogen, trifluoromethyl or methyl, or one of R₁₃ and R₁₄ is cyano and the other is hydrogen or methyl, or -C(R₁₃R₁₄) is a cyclopropyl group, or Z is nitrogen or CH and forms a five or six membered heterocyclic ring fused with R₅, which ring optionally comprises two or three further hetero members selected independently from oxygen, nitrogen, NR₁₂, and S(O)_m, and optionally comprises from one to three double bonds, and is optionally substituted with halo, C₁-C₄ alkyl, -O(C₁-C₄ alkyl), NH₂, NHCH₃, N(CH₃)₂, CF₃, or OCF₃, with the proviso that said ring does not contain any -S-S-, -S-O-, -N-S-, or -O-O- bonds, and does not comprise more than two oxygen or S(O)_m heterologous members;

R₁ is C(O)H, C(O)(C₁-C₆ alkyl), C(O)(C₁-C₆ alkylene)(C₃-C₈ cycloalkyl), C(O)(C₃-C₈ cycloalkylene)(C₃-C₈ cycloalkyl), C(O)(C₁-C₆ alkylene)(C₄-C₈ heterocycloalkyl), -C(O)(C₃-C₈ cycloalkylene)(C₄-C₈ heterocycloalkyl), C₁-C₈ alkyl, C₃-C₈ cycloalkyl, C₄-C₈ heterocycloalkyl, -(C₁-C₆ alkylene)(C₃-C₈ cycloalkyl), -(C₃-C₈ cycloalkylene)(C₃-C₈ cycloalkyl), -(C₁-C₆ alkylene)(C₄-C₈ heterocycloalkyl), -(C₃-C₈ cycloalkylene)(C₄-C₈ heterocycloalkyl), or -O-aryl, or -O-(C₁-C₆ alkylene)-aryl; wherein said aryl, C₄-C₈ heterocycloalkyl, C₁-C₈ alkyl, C₃-C₈ cycloalkyl, C₃-C₂ cycloalkylene, and C₁-C₆ alkylene groups may each independently be optionally substituted with from one to six fluoro and may each independently be optionally substituted with one or two substituents R₈ independently selected from the group consisting of C₁-C₄ alkyl, -C₃-C₈ cycloalkyl, hydroxy, chloro, bromo, iodo, CF₃, -O-(C₁-C₆ alkyl), -O-(C₃-C₈ cycloalkyl), -O-CO-(C₁-C₄ alkyl), -O-CO-NH(C₁-C₄ alkyl), -O-CO-N(R₂₄)(R₂₅), -N(R₂₄)(R₂₅), -S(C₁-C₄ alkyl), -S(C₃-C₈ cycloalkyl), -N(C₁-C₄ alkyl)CO(C₁-C₄ alkyl), -NHCO(C₁-C₄ alkyl), -COO(C₁-C₄ alkyl), -CONH(C₁-C₄ alkyl), -CON(C₁-C₄ alkyl)(C₁-C₂ alkyl), CN, NO₂, -OSO₂(C₁-C₄ alkyl), S⁺(C₁-C₆ alkyl)(C₁-C₂ alkyl)⁻, -SO(C₁-C₄ alkyl) and -SO₂(C₁-C₄ alkyl); and wherein the C₁-C₆ alkyl, C₁-C₆ alkylene, C₃-C₈ cycloalkyl, C₃-C₈ cycloalkylene, and C₃-C₈ heterocycloalkyl moieties of R₁ may optionally independently contain from one to three double or triple bonds; and wherein the C₁-C₄ alkyl

moieties and C₁-C₆ alkyl moieties of R₈ can optionally independently be substituted with hydroxy, amino, C₁-C₄ alkyl, aryl, -CH₂-aryl, C₃-C₅ cycloalkyl, or -O-(C₁-C₄ alkyl), and can optionally independently be substituted with from one to six fluoro, and can optionally contain one or two double or triple bonds; and wherein each heterocycloalkyl group of R₁ contains from

- 5 one to three heteroatoms selected from oxygen, S(O)_m, nitrogen, and NR₁₂:

R₂ is hydrogen, C₁-C₁₂ alkyl, C₃-C₈ cycloalkyl, C₄-C₈ heterocycloalkyl, -(C₁-C₆ alkylene)(C₃-C₈ cycloalkyl), -(C₃-C₈ cycloalkylene)(C₃-C₈ cycloalkyl), -(C₁-C₆ alkylene)(C₄-C₈ heterocycloalkyl), -(C₃-C₈ cycloalkylene)(C₄-C₈ heterocycloalkyl), aryl, -(C₁-C₆ alkylene)aryl, or -(C₃-C₈ cycloalkylene)aryl; wherein each of the foregoing R₂ groups may optionally be
10 substituted with from one to three substituents independently selected from chloro, fluoro, and C₁-C₆ alkyl, wherein one of said one to three substituents can further be selected from bromo, iodo, C₁-C₆ alkoxy, -OH, -O-CO-(C₁-C₆ alkyl), -O-CO-N(C₁-C₄ alkyl)(C₁-C₂ alkyl), -S(C₁-C₆ alkyl), -S(O)(C₁-C₆ alkyl), -S(O)₂(C₁-C₆ alkyl), S'(C₁-C₆ alkyl)(C₁-C₂ alkyl)', CN, and NO₂; and wherein
15 the C₁-C₁₂ alkyl, -(C₁-C₆ alkylene), -(C₃-C₈ cycloalkyl), -(C₃-C₈ cycloalkylene), and -(C₅-C₈ heterocycloalkyl) moieties of R₂ may optionally independently contain from one to three double or triple bonds; and wherein each heterocycloalkyl group of R₂ contains from one to three heteroatoms selected from oxygen, S(O)_m, nitrogen, and NR₁₂:

or when R₁ and R₂ are as in -NHCHR₁R₂, -OCHR₁R₂, -SCHR₁R₂, -CHR₁R₂ or -NR₁R₂, R₁ and R₂ of B may form a saturated 5- to 8-membered ring which may optionally contain one or
20 two double bonds and in which one or two of the ring carbons may optionally be replaced by an oxygen, S(O)_m, nitrogen or NR₁₂; and which carbocyclic ring can optionally be substituted with from 1 to 3 substituents selected from the group consisting of hydroxy, C₁-C₄ alkyl, fluoro, chloro, bromo, iodo, CF₃, -O-(C₁-C₄ alkyl), -O-CO-(C₁-C₄ alkyl), -O-CO-NH(C₁-C₄ alkyl), -O-CO-N(C₁-C₄ alkyl)(C₁-C₂ alkyl), -NH(C₁-C₄ alkyl), -N(C₁-C₂ alkyl)(C₁-C₄ alkyl), -S(C₁-C₄ alkyl), -N(C₁-C₄ alkyl)CO(C₁-C₄ alkyl), -NHCO(C₁-C₄ alkyl), -COO(C₁-C₄ alkyl), -CONH(C₁-C₄ alkyl), -CON(C₁-C₄ alkyl)(C₁-C₂ alkyl), CN, NO₂, -OSO₂(C₁-C₄ alkyl), -SO(C₁-C₄ alkyl), and -SO₂(C₁-C₄ alkyl),
25 wherein one of said one to three substituents can further be selected from phenyl;

R₃ is methyl, ethyl, fluoro, chloro, bromo, iodo, cyano, methoxy, OCF₃, NH₂, NH(C₁-C₂ alkyl), N(CH₃)₂, -NHCOCF₃, -NHCH₂CF₃, S(O)_m(C₁-C₄ alkyl), CONH₂, -CONHCH₃, CON(CH₃)₂,
30 -CF₃, or CH₂OCH₃;

R₄ is hydrogen, C₁-C₄ alkyl, C₃-C₅ cycloalkyl, -(C₁-C₄ alkylene)(C₃-C₅ cycloalkyl), -(C₃-C₅ cycloalkylene)(C₃-C₅ cycloalkyl), cyano, fluoro, chloro, bromo, iodo, -OR₂₄, C₁-C₆ alkoxy, -O-(C₃-C₅ cycloalkyl), -O-(C₁-C₄ alkylene)(C₃-C₅ cycloalkyl), -O-(C₃-C₅ cycloalkylene)(C₃-C₅ cycloalkyl), -CH₂SC(S)O(C₁-C₄ alkyl), -CH₂OCF₃, CF₃, amino, nitro, -NR₂₄R₂₅, -(C₁-C₄ alkylene)-OR₂₄, -(C₁-C₄ alkylene)Cl, -(C₁-C₄ alkylene)NR₂₄R₂₅, -NHCOR₂₄, -NHCONR₂₄R₂₅, -C=NOR₂₄, -NHNR₂₄R₂₅, -S(O)_mR₂₄, -C(O)R₂₄, -OC(O)R₂₄, -C(O)CN, -C(O)NR₂₄R₂₅, -C(O)NHN₂₄R₂₅, and -

COOR_{24} , wherein the alkyl and alkylene groups of R_4 may optionally independently contain one or two double or triple bonds and may optionally independently be substituted with one or two substituents R_{10} , independently selected from hydroxy, amino, $-\text{NHCOCH}_3$, $-\text{NHCOCH}_2\text{Cl}$, $-\text{NH}(\text{C}_1\text{-C}_2 \text{ alkyl})$, $-\text{N}(\text{C}_1\text{-C}_2 \text{ alkyl})(\text{C}_1\text{-C}_2 \text{ alkyl})$, $-\text{COO}(\text{C}_1\text{-C}_4 \text{ alkyl})$, $-\text{COOH}$, $-\text{CO}(\text{C}_1\text{-C}_4 \text{ alkyl})$, $\text{C}_1\text{-C}_8$ alkoxy, $\text{C}_1\text{-C}_3$ thioalkyl, cyano and nitro, and with one to four substituents independently selected from fluoro and chloro;

5 R_5 is aryl or heteroaryl and is substituted with from one to four substituents R_{27} independently selected from halo, $\text{C}_1\text{-C}_{10}$ alkyl, $-(\text{C}_1\text{-C}_4 \text{ alkylene})(\text{C}_3\text{-C}_8 \text{ cycloalkyl})$, $-(\text{C}_1\text{-C}_4 \text{ alkylene})(\text{C}_4\text{-C}_8 \text{ heterocycloalkyl})$, $-(\text{C}_3\text{-C}_8 \text{ cycloalkyl})$, $-(\text{C}_4\text{-C}_8 \text{ heterocycloalkyl})$, $-(\text{C}_3\text{-C}_8 \text{ cycloalkylene})(\text{C}_3\text{-C}_8 \text{ cycloalkyl})$, $-(\text{C}_3\text{-C}_8 \text{ cycloalkylene})(\text{C}_4\text{-C}_8 \text{ heterocycloalkyl})$, $\text{C}_1\text{-C}_4$ haloalkyl, $\text{C}_1\text{-C}_4$ haloalkoxy, nitro, cyano, $-\text{NR}_{24}\text{R}_{25}$, $-\text{NR}_{24}\text{CO}_2\text{R}_{26}$, $-\text{COR}_{24}$, $-\text{OR}_{25}$, $-\text{CONR}_{24}\text{R}_{25}$, $-\text{CO}(\text{NOR}_{22})\text{R}_{23}$, $-\text{CO}_2\text{R}_{26}$, $\text{C}=\text{N}(\text{OR}_{22})\text{R}_{23}$, and $-\text{S}(\text{O})_m\text{R}_{23}$; wherein said $\text{C}_1\text{-C}_{10}$ alkyl, $\text{C}_3\text{-C}_8$ cycloalkyl, $(\text{C}_1\text{-C}_4 \text{ alkylene})$, $(\text{C}_3\text{-C}_8 \text{ cycloalkyl})$, $(\text{C}_3\text{-C}_8 \text{ cycloalkylene})$, and $(\text{C}_4\text{-C}_8 \text{ heterocycloalkyl})$ groups can be optionally substituted with from one to three substituents independently selected from $\text{C}_1\text{-C}_4$ alkyl, $\text{C}_3\text{-C}_8$ cycloalkyl, $(\text{C}_1\text{-C}_4 \text{ alkylene})(\text{C}_3\text{-C}_8 \text{ cycloalkyl})$, $-(\text{C}_3\text{-C}_8 \text{ cycloalkylene})(\text{C}_3\text{-C}_8 \text{ cycloalkyl})$, $\text{C}_1\text{-C}_4$ haloalkyl, hydroxy, $\text{C}_1\text{-C}_8$ alkoxy, nitro halo, cyano, $-\text{NR}_{24}\text{R}_{25}$, $-\text{NR}_{24}\text{COR}_{25}$, $-\text{NR}_{24}\text{CO}_2\text{R}_{26}$, $-\text{COR}_{24}$, $-\text{OR}_{25}$, $-\text{CONR}_{24}\text{R}_{25}$, $-\text{CO}_2\text{R}_{26}$, $-\text{CO}(\text{NOR}_{22})\text{R}_{25}$, and $-\text{S}(\text{O})_m\text{R}_{23}$; and wherein two adjacent substituents of the R_5 group can optionally form a 5-7 membered ring, saturated or unsaturated, fused to R^5 , which ring optionally can contain one, two, or three heterologous members independently selected from O, S(O)_m, and N, but not any -S-S-, -O-O-, -S-O-, or -N-S- bonds, and which ring is optionally substituted with $\text{C}_1\text{-C}_4$ alkyl, $\text{C}_3\text{-C}_8$ cycloalkyl, $-(\text{C}_1\text{-C}_4 \text{ alkylene})(\text{C}_3\text{-C}_8 \text{ cycloalkyl})$, $-(\text{C}_3\text{-C}_8 \text{ cycloalkylene})(\text{C}_3\text{-C}_8 \text{ cycloalkyl})$, $\text{C}_1\text{-C}_4$ haloalkyl, nitro, halo, cyano $-\text{NR}_{24}\text{R}_{25}$, $-\text{NR}_{24}\text{COR}_{25}$, $-\text{NR}_{24}\text{CO}_2\text{R}_{26}$, $-\text{COR}_{24}$, $-\text{OR}_{25}$, $-\text{CONR}_{24}\text{R}_{25}$, $-\text{CO}_2\text{R}_{26}$, $-\text{CO}(\text{NOR}_{22})\text{R}_{25}$, or $-\text{S}(\text{O})_m\text{R}_{23}$; wherein one of said one to four optional substituents R_{27} can further be selected from $-\text{SO}_2\text{NH}(\text{C}_1\text{-C}_4 \text{ alkyl})$, $-\text{SO}_2\text{NH}(\text{C}_1\text{-C}_4 \text{ alkylene})(\text{C}_3\text{-C}_8 \text{ cycloalkyl})$, $-\text{SO}_2\text{NH}(\text{C}_3\text{-C}_8 \text{ cycloalkylene})(\text{C}_3\text{-C}_8 \text{ cycloalkyl})$, $-\text{SO}_2\text{N}(\text{C}_1\text{-C}_4 \text{ alkyl})(\text{C}_1\text{-C}_2 \text{ alkyl})$, $-\text{SO}_2\text{NH}_2$, $-\text{NHSO}_2(\text{C}_1\text{-C}_4 \text{ alkyl})$, $-\text{NHSO}_2(\text{C}_3\text{-C}_8 \text{ cycloalkyl})$, $-\text{NHSO}_2(\text{C}_1\text{-C}_4 \text{ alkylene})(\text{C}_3\text{-C}_8 \text{ cycloalkyl})$, and $-\text{NHSO}_2(\text{C}_3\text{-C}_8 \text{ cycloalkylene})(\text{C}_3\text{-C}_8 \text{ cycloalkyl})$; and wherein the alkyl, and alkylene groups of R_5 may independently optionally contain one double or triple bond;

10 R_6 is hydrogen, $\text{C}_1\text{-C}_8$ alkyl, $\text{C}_3\text{-C}_8$ cycloalkyl, $-(\text{C}_1\text{-C}_6 \text{ alkylene})(\text{C}_3\text{-C}_8 \text{ cycloalkyl})$, or $-(\text{C}_3\text{-C}_8 \text{ cycloalkylene})(\text{C}_3\text{-C}_8 \text{ cycloalkyl})$, wherein said alkyl and cycloalkyl may optionally be substituted with one hydroxy, methoxy, ethoxy or fluoro group;

15 or, wherein the compound is a compound of formula II, R_6 and R_4 can together form an oxo (=O) group, or can be connected to form a 3-8 membered carbocyclic ring, optionally containing one to three double bonds, and optionally containing one, two, or three heterologous

ring members selected from O, SO_m, N, and NR₁₂, but not containing any -O-O-, -S-O-, -S-S-, or -N-S- bonds, and further optionally substituted with C₁-C₄ alkyl or C₃-C₈ cycloalkyl, wherein said C₁-C₄ alkyl substituent may optionally contain one double or triple bond;

- R₇ is hydrogen, methyl, fluoro, chloro, bromo, iodo, cyano, hydroxy, -O(C₁-C₂ alkyl), -O(cyclopropyl), -COO(C₁-C₂ alkyl), -COO(C₃-C₈ cycloalkyl), -OCF₃, CF₃, -CH₂OH, or CH₂OCH₃;
- 5 R₁₁ is hydrogen, hydroxy, fluoro, ethoxy, or methoxy;
- R₁₂ is hydrogen or C₁-C₄ alkyl;
- R₁₆ and R₁₇ are each, independently, hydrogen, hydroxy, methyl, ethyl, methoxy, or ethoxy, except that R₁₆ and R₁₇ are not both methoxy or ethoxy;
- 10 or R₁₆ and R₁₇ together form an oxo (=O) group;
- or R₁₆ and R₁₇ are connected to form a 3-8 membered carbocyclic ring, optionally containing one to three double bonds, and optionally containing from one to three heterologous ring members selected from O, SO_m, N, and NR₁₂, but not containing any -O-O-, -S-O-, -S-S-, or -N-S- bonds, and further optionally substituted with C₁-C₄ alkyl or C₃-C₈ cycloalkyl, wherein
- 15 said C₁-C₄ alkyl substituent may optionally contain one double or triple bond;
- R₂₂ is independently at each occurrence selected from hydrogen, C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₃-C₈ alkenyl, C₃-C₈ alkynyl, C₃-C₈ cycloalkyl, (C₃-C₈ cycloalkylene)(C₃-C₈ cycloalkyl), and (C₁-C₄ alkylene)(C₃-C₈ cycloalkyl);
- R₂₃ is independently at each occurrence selected from C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₂-C₈ alkoxyalkyl, C₃-C₈ cycloalkyl, -(C₁-C₄ alkylene)(C₃-C₈ cycloalkyl), -(C₃-C₈ cycloalkylene)(C₃-C₈ cycloalkyl), aryl, -(C₁-C₄ alkylene)aryl, piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine, and thiomorpholine;
- 20 R₂₄ and R₂₅ are independently at each occurrence selected from hydrogen, -C₁-C₄ alkyl, C₁-C₄ haloalkyl, especially CF₃, -CHF₂, CF₂CF₃, or CH₂CF₃, -(C₁-C₄ alkylene)OH, -(C₁-C₄ alkylene)-O-(C₁-C₄ alkyl), -(C₁-C₄ alkylene)-O-(C₃-C₈ cycloalkyl), C₃-C₈ cycloalkyl, -(C₁-C₄ alkylene)(C₃-C₈ cycloalkyl), -(C₃-C₈ cycloalkylene)(C₃-C₈ cycloalkyl), -C₄-C₈ heterocycloalkyl, -(C₁-C₄ alkylene)(C₄-C₈ heterocycloalkyl), -(C₃-C₈ cycloalkylene)(C₄-C₈ heterocycloalkyl), aryl, and -(C₁-C₄ alkylene)(aryl), wherein the -C₄-C₈ heterocycloalkyl groups can each independently optionally be substituted with aryl, CH₂aryl, or C₁-C₄ alkyl, and can optionally contain one or
- 25 two double or triple bonds; or, when R₂₄ and R₂₅ are as NR₂₄R₂₅, -C(O)NR₂₄R₂₅, -(C₁-C₄ alkylene)NR₂₄R₂₅, or -NHCONR₂₄R₂₅, then NR₂₄R₂₅ may further optionally form a 4 to 8 membered heterocyclic ring optionally containing one or two further hetero members independently selected from S(O)_m, oxygen, nitrogen, and NR₁₂, and optionally containing from one to three double bonds;
- 30

R_{28} is independently at each occurrence selected from C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_3-C_8 cycloalkyl, $-(C_1-C_4$ alkylene) $(C_3-C_8$ cycloalkyl), $-(C_3-C_8$ cycloalkylene) $(C_3-C_8$ cycloalkyl), aryl, and $-(C_1-C_4$ alkylene)(aryl); and

wherein each m is independently zero, one, or two.

- 5 with the proviso that heterocycloalkyl groups of the compound of formula I, II, or III do not comprise any $-S-S-$, $-S-O-$, $-N-S-$, or $-O-O-$ bonds, and do not comprise more than two oxygen or $S(O)_m$ heterologous members.
2. A compound according to claim 1, wherein R_4 is $-NHCH_2CF_3$, $-CONHNH_2$, $-CONHNHCH_3$, $-OCF_3$, fluoro, $-OCHF_2$, $-OCH_2(C_3-C_8$ cycloalkyl), $-O-(C_3-C_8$ cycloalkyl), $10 SCH_2(C_3-C_8$ cycloalkyl), $-S(C_3-C_8$ cycloalkyl), $-OCH_3$, $-CH_3$, $-CH_2CH_3$, chloro, bromo, $-CF_3$, $-CH_2OH$, $-CH_2OCH_3$, $-CH_2OCF_3$, $-SCH_3$, $-S(O)CH_3$, $-S(O)_2CH_3$, $-C(O)CH_3$, $-NR_{24}R_{25}$, $-NO_2$, $-CH(OH)CH_3$, or $-CN$.
- 15 3. A compound according to claim 1, wherein R_4 is $-C(O)NR_{24}R_{25}$ or $-C(O)NHNR_{24}R_{25}$.
4. A compound according to claim 3, wherein R_{24} and R_{25} are selected independently from hydrogen and $-C_1-C_4$ alkyl.
5. A compound according to claim 1, wherein R_4 is $-(C_1-C_4$ alkylene) $NR_{24}R_{25}$.
6. A compound according to claim 1, wherein R_4 is $-COOCH_3$ or $-COOCH_2CH_3$.
7. A compound according to claim 6, wherein R_4 is $-COOCH_3$.
- 20 8. A compound of formula I according to claim 1, wherein Z is O; B is $-NHCHR_1R_2$, wherein R_1 is $-C(O)H$, $-C(O)(C_1-C_8$ alkyl), or $-C_1-C_6$ alkyl, wherein said C_1-C_6 alkyl is optionally substituted with from one to six fluoro atoms or one or two R_8 independently selected from $-C_1-C_4$ alkyl, hydroxy and $-O-(C_1-C_8$ alkyl), and wherein R_2 is $-C_1-C_{12}$ alkyl optionally containing from one to three double or triple bonds and optionally substituted with from one to three substituents selected from fluoro and C_1-C_8 alkyl; R_5 is phenyl, pyridyl or pyrimidyl, substituted with two or three R_{27} groups selected from halo, $-(C_1-C_4$ haloalkyl), $-C(O)R_{24}$, $-OR_{25}$, $-C(O)NR_{24}R_{25}$, and C_5-C_{10} alkyl which is optionally substituted with one to three substituents, preferably one substituent, selected from hydroxy, C_1-C_8 alkoxy, and $-NR_{24}R_{25}$; and R_4 is $-C(O)NR_{24}R_{25}$.
- 25 9. A compound of formula I according to claim 1, wherein Z is O; B is $-NHCHR_1R_2$, wherein R_1 of $-NHCHR_1R_2$ is $-C(O)H$, $-C(O)(C_1-C_8$ alkyl), or $-C_1-C_6$ alkyl, wherein said C_1-C_6 alkyl is optionally substituted with from one to six fluoro atoms or one or two R_8 independently selected from $-C_1-C_4$ alkyl, hydroxy and $-O-(C_1-C_8$ alkyl), and wherein R_2 of $-NHCHR_1R_2$ is $-C_1-C_{12}$ alkyl optionally containing from one to three double or triple bonds and optionally substituted with from one to three substituents selected from fluoro and C_1-C_8 alkyl; R_5 is phenyl, pyridyl or pyrimidyl, substituted with two or three R_{27} groups selected

from halo, -(C₁-C₄ haloalkyl), -C(O)R₂₄, -OR₂₅, -C(O)NR₂₄R₂₅, and C₁-C₁₀ alkyi which is optionally substituted with one to three substituents, preferably one substituent, selected from hydroxy, C₁-C₆ alkoxy, and -NR₂₄R₂₅; and R₄ is -NR₁R₂, wherein R₁ of -NR₁R₂ is C₁-C₆ alkyl, C₃-C₈ cycloalkyl, or -(C₁-C₆ alkylene)(C₃-C₈ cycloalkyl), and R₂ of -NR₁R₂ is C₁-C₁₂ alkyl 5 optionally containing from one to three double or triple bonds and optionally substituted with from one three fluoro atoms.

10. A compound according to claim 1 selected from:

- 2-(4-chloro-2,6-dimethyl-phenoxy)-4-(1-hydroxymethyl-propylamino)-6,N-dimethyl-nicotinamide;
- 10 2-(4-chloro-2,6-dimethyl-phenoxy)-4-(1-methoxymethyl-propylamino)-6,N-dimethyl-nicotinamide;
- 2-(4-chloro-2,6-dimethyl-phenoxy)-4-(1-methoxymethyl-propylamino)-6-methyl-nicotinamide;
- 15 2-(4-bromo-2-methoxy-phenoxy)-4-(1-ethyl-propylamino)-6-methyl-nicotinamide;
- 2-(4-chloro-2,6-dimethyl-phenoxy)-4-(1-ethyl-2-methoxy-propylamino)-6-methyl-nicotinamide;
- 2-(4-chloro-2,6-dimethyl-phenoxy)-4-(1-ethyl-2-methoxy-propylamino)-6,N-dimethyl-nicotinamide;
- 20 2-(4-chloro-2-trifluoromethoxy-phenoxy)-4-(1-ethyl-propylamino)-6-methyl-nicotinamide;
- 2-(4-chloro-2-trifluoromethoxy-phenoxy)-4-(1-ethyl-propylamino)-6-N-dimethyl-nicotinamide;
- 25 2-(4-chloro-2,6-dimethyl-phenoxy)-4-(1S,2R-1-ethyl-2-methoxy-propylamino)-6,N-dimethyl-nicotinamide;
- 2-(4-chloro-2,6-dimethyl-phenoxy)-4-(1S,2S-1-ethyl-2-methoxy-propylamino)-6,N-dimethyl-nicotinamide;
- 2-(4-bromo-2-methoxy-phenoxy)-4-(1-ethyl-propylamino)-6-methyl-nicotinonitrile;
- 4-[4-(1-ethyl-propoxy)-3,6-dimethyl-pyridin-2-yloxy]-3,5-dimethyl-benzamide;
- 2-(4-chloro-2,6-dimethyl-phenoxy)-6-methyl-4-(1-methylsulfanyl)methyl-propylamino)-30 nicotinic acid methyl ester;
- 2-(4-chloro-2,6-dimethyl-phenoxy)-4-(1-hydroxymethyl-propylamino)-6-methyl-nicotinic acid methyl ester;
- 2-(4-bromo-2,6-dimethyl-phenoxy)-4-(1-ethyl-propylamino)-6-methyl-nicotinonitrile;
- 2-(4-chloro-2-trifluoromethoxy-phenoxy)-4-(1-ethyl-propylamino)-6-methyl-nicotinic 35 acid methyl ester; and

2-(4-chloro-2,6-dimethyl-phenoxy)-6-methyl-4-(tetrahydro-furan-3-ylamino)-nicotinic acid methyl ester;

and pharmaceutically acceptable salts thereof.

11. A pharmaceutical composition for the treatment of (a) a disorder or condition
5 the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitated by CRF, or (b) a disorder or condition selected from inflammatory disorders such as rheumatoid arthritis and osteoarthritis, pain, asthma, psoriasis and allergies; generalized anxiety disorder; panic; phobias, including social phobia, agoraphobia, and specific phobias; obsessive-compulsive disorder; post-traumatic stress
10 disorder; sleep disorders induced by stress; pain perception such as fibromyalgia; mood disorders such as depression, including major depression, single episode depression, recurrent depression, child abuse induced depression, mood disorders associated with premenstrual syndrome, and postpartum depression; dysthemia; bipolar disorders; cyclothymia; chronic fatigue syndrome; stress-induced headache; cancer; irritable bowel
15 syndrome, Crohn's disease; spastic colon; post operative ileus; ulcer; diarrhea; stress-induced fever; human immunodeficiency virus infections; neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and Huntington's disease; gastrointestinal diseases; eating disorders such as anorexia and bulimia nervosa; hemorrhagic stress; chemical dependencies or addictions, including dependencies or addictions to alcohol,
20 cocaine, heroin, benzodiazapines, or other drugs; drug or alcohol withdrawal symptoms; stress-induced psychotic episodes; euthyroid sick syndrome; syndrome of inappropriate antidiuretic hormone; obesity; infertility; head trauma; spinal cord trauma; ischemic neuronal damage, including cerebral ischemia, for example cerebral hippocampal ischemia; excitotoxic neuronal damage; epilepsy; stroke; immune dysfunctions including stress induced immune
25 dysfunctions, including porcine stress syndrome, bovine shipping fever, equine paroxysmal fibrillation, confinement dysfunction in chicken, sheering stress in sheep, and human-animal interaction stress in dogs; muscular spasms; urinary incontinence; senile dementia of the Alzheimer's type; multiinfarct dementia; amyotrophic lateral sclerosis; hypertension; tachycardia; congestive heart failure; osteoporosis; premature birth; hypoglycemia, and
30 Syndrome X in a mammal or bird, comprising an amount of a compound according to claim 1 that is effective in the treatment of such disorder or condition, and a pharmaceutically acceptable carrier.

12. A method for the treatment of (a) a disorder or condition the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders
35 induced or facilitated by CRF, or (b) a disorder or condition selected from inflammatory disorders such as rheumatoid arthritis and osteoarthritis, pain, asthma, psoriasis and

allergies; generalized anxiety disorder; panic; phobias, including social phobia, agoraphobia, and specific phobias; obsessive-compulsive disorder; post-traumatic stress disorder; sleep disorders induced by stress; pain perception such as fibromyalgia; mood disorders such as depression, including major depression, single episode depression, recurrent depression,
5 child abuse induced depression, mood disorders associated with premenstrual syndrome, and postpartum depression; dysthemia; bipolar disorders; cyclothymia; chronic fatigue syndrome; stress-induced headache; cancer; irritable bowel syndrome, Crohn's disease; spastic colon; post operative ileus; ulcer; diarrhea; stress-induced fever; human immunodeficiency virus infections; neurodegenerative diseases such as Alzheimer's disease,
10 Parkinson's disease and Huntington's disease; gastrointestinal diseases; eating disorders such as anorexia and bulimia nervosa; hemorrhagic stress; chemical dependencies or addictions, including dependencies or addictions to alcohol, cocaine, heroin, benzodiazapines, or other drugs; drug or alcohol withdrawal symptoms; stress-induced psychotic episodes; euthyroid sick syndrome; syndrome of inappropriate antidiuretic
15 hormone; obesity; infertility; head trauma; spinal cord trauma; ischemic neuronal damage, including cerebral ischemia, for example cerebral hippocampal ischemia; excitotoxic neuronal damage; epilepsy; stroke; immune dysfunctions including stress induced immune dysfunctions, including porcine stress syndrome, bovine shipping fever, equine paroxysmal fibrillation, confinement dysfunction in chicken, sheering stress in sheep, and human-animal
20 interaction stress in dogs; muscular spasms; urinary incontinence; senile dementia of the Alzheimer's type; multiinfarct dementia; amyotrophic lateral sclerosis; hypertension; tachycardia; congestive heart failure; osteoporosis; premature birth; hypoglycemia, and Syndrome X in a mammal or bird, comprising administering to a subject in need of said treatment an amount of a compound according to claim 1, that is effective in treating such
25 disorder or condition.

13. A method of treating a condition comprising administering a compound of claim 1 in an amount effective to treat said condition, wherein said condition is selected from the group consisting of:

- a) abnormal circadian rhythm;
- b) depression, further wherein a second compound for treating depression is administered, said second compound for treating depression having an onset of action that is delayed with respect to that of said CRF antagonist; and
- c) emesis.

35 14. The method of claim 13 wherein the condition is abnormal circadian rhythm, and the compound is combined with a second compound useful for treating a sleep disorder.

15. The method of claim 14, wherein said second compound is selected from the group consisting of tachykinin antagonists, agonists for GABA brain receptors, metalonergic compounds, GABA brain receptor agonists, 5HT₂ receptor antagonists, and D4 receptor binding.
- 5 16. The method of claim 13 wherein said condition is depression, and wherein said second compound having delayed action for treating depression is selected from the group consisting of selective serotonin reuptake inhibitors, tricyclic antidepressants, norepinephrine uptake inhibitors, lithium, bupropion, sertraline, fluoxetine, trazodone, and a tricyclic antidepressant selected from the group consisting of imipramine, amitriptyline, 10 trimipramine, doxepin, desipramine, nortriptyline, protriptyline, amoxapine, clomipramine, maprotiline, and carbamazepine, and pharmaceutically acceptable salts and esters of the above-recited compounds.
17. The method of claim 13 wherein said condition is emesis, further comprising administering a second compound for treating emesis.
- 15 18. The method of claim 17 wherein said second compound for treating emesis is selected from the group consisting of tachykinin antagonists, 5HT3 antagonists, GABA agonists, and substance P inhibitors.
19. A pharmaceutical composition for treating a condition comprising a compound of claim 1 in an amount effective to treat said condition and a pharmaceutically acceptable carrier, wherein said condition is selected from the group consisting of:
- 20 a) abnormal circadian rhythm;
- b) depression, further wherein a second compound for treating depression is administered, said second compound for treating depression having an onset of action that is delayed with respect to that of said CRF antagonist; and
- 25 c) emesis.
20. A pharmaceutical composition according to claim 19, wherein the condition is abnormal circadian rhythm, and the compound is combined with a second compound useful for treating a sleep disorder.
- 30 21. A pharmaceutical composition according to claim 20, wherein said second compound is selected from the group consisting of tachykinin antagonists, agonists for GABA brain receptors, metalonergic compounds, GABA brain receptor agonists, 5HT₂ receptor antagonists, and D4 receptor binding.
22. A pharmaceutical composition according to claim 19 wherein said condition is 35 depression, and wherein said second compound having delayed action for treating depression is selected from the group consisting of selective serotonin reuptake inhibitors,

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tricyclic antidepressants, norepinephrine uptake inhibitors, lithium, bupropion, sertraline, fluoxetine, trazodone, and a tricyclic antidepressant selected from the group consisting of imipramine, amitriptyline, trimipramine, doxepin, desipramine, nortriptyline, protriptyline, amoxapine, clomipramine, maprotiline, and carbamazepine, and pharmaceutically acceptable

- 5 salts and esters of the above-recited compounds.

23. A pharmaceutical composition according to claim 19 wherein said condition is emesis, further comprising administering a second compound for treating emesis.

24. A pharmaceutical composition according to claim 23 wherein said second compound for treating emesis is selected from the group consisting of tachykinin antagonists,
10 5HT3 antagonists, GABA agonists, and substance P inhibitors.

INTERNATIONAL SEARCH REPORT

PCT/IB 01/00004

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7	C07D213/74	C07D213/643	C07D213/80	C07D213/82	C07D239/48
	C07D239/47	C07D487/04	C07D473/34	A61K31/44	A61K31/52
	A61K31/505	A61P43/00	//(C07D487/04, 235:00, 221:00)		

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, EPO-Internal, WPI Data, PAJ, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	EP 1 059 100 A (PFIZER PRODUCTS INC., USA) 13 December 2000 (2000-12-13) the whole document	1-8, 10-23
P, X	EP 1 040 831 A (PFIZER PRODUCTS INC., USA) 4 October 2000 (2000-10-04) page X	1-8, 10-23
X	CHHABRIA, MAHESH. T. ET AL: "Synthesis of some 4-bromopyrimidines and condensed 4-bromopyrimidines by one-pot reactions" HETEROCYCLES (1999), 51(11), 2723-2729 , XP000994941 see Table 1	1
	-/-	

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *Z* document member of the same patent family

Date of the actual completion of the international search

3 April 2001

Date of mailing of the international search report

24.04.01

Name and mailing address of the ISA

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Authorized officer

Scruton-Evans, I

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 951 906 A (PFIZER PRODUCTS INC., JAPAN) 27 October 1999 (1999-10-27) cited in the application the whole document ----	1,2, 10-23
X	WO 95 33750 A (PFIZER INC., USA) 14 December 1995 (1995-12-14) the whole document ----	1-8, 10-23 1-23
X	EP 0 773 023 A (PFIZER INC., USA) 14 May 1997 (1997-05-14) the whole document ----	1
X	DEMINA, L. M. ET AL: "Alkylamides of 2-chloro- and 2-arylamino-4,6-dimethylnicotinic acid: synthesis and anticonvulsant activity" KHIM.-FARM. ZH. (1993), 27(7), 34-5 , XP000994919 see formula II ----	1-4
X	DEMINA, L. M. ET AL: "Synthesis of amides of 2-(arylamino)-4,6-dimethylnicotinic acids" KHIM. GETEROTSIKL. SOEDIN. (1992), (11), 1506-8 , XP000994890 see formula I ----	1,3,4
X	KAMEL, M. M. ET AL: "New pyrimidine-Mannich bases of possible schistosomicidal activity" PHARMAZIE (1990), 45(2), 139-40 , XP000986005 see formula 4 ----	1
Y	WO 94 13676 A (PFIZER ;CHEN YUHPYNG L (US)) 23 June 1994 (1994-06-23) the whole document ----	1-23
X	WO 95 10506 A (DU PONT MERCK PHARMA) 20 April 1995 (1995-04-20) the whole document ----	1

INTERNATIONAL SEARCH REPORTInternational application No.
PCT/IB 01/00004**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 11-17 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.: 1,2,10-23(partly)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
- No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1,2,10-23(partly)

Present claims 1,2,10-23. relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. There are no examples of formula II compounds, and only 9 examples of formula III. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds of the examples, and the general formula I wherein Z is O or NH, R5 is phenyl or pyridyl, R3 is Me and R4 is as in claims 3-8 or 1-ethylpropoxy

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date	
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